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118 pages | 6 x 9 | PAPERBACK

ISBN 978-0-309-70352-9 | DOI 10.17226/27056

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SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine. 2023. *Sponsor Influences on the Quality and Independence of Health Research: Proceedings of a Workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/27056.

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Sponsor Influences on the Quality and Independence of Health Research

Dara Rosenberg, Elizabeth Boyle, Alexandra McKay, and Joe Alper, *Rapporteurs*

Board on Population Health and Public Health Practice

Board on Health Sciences Policy

Health and Medicine Division

Proceedings of a Workshop

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This activity was supported by contracts between the National Academy of Sciences and the Gordon and Betty Moore Foundation and Rita Allen Foundation. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-XXXXX-X
International Standard Book Number-10: 0-309-XXXXX-X
Digital Object Identifier: https://doi.org/10.17226/27056

This publication is available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

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Printed in the United States of America.

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2023. *Sponsor influences on the quality and independence of health research: A workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/27056.

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Reviewers

This Proceedings of a Workshop was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine (the National Academies) in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We thank the following individuals for their review of this proceedings:

ARAMANDLA RAMESH, Meharry Medical College
GARY RUSKIN, U.S. Right to Know

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by Lawrence J. Appel, Johns Hopkins University. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

We also thank staff member Jennifer Heimberg for reading and providing helpful comments on this manuscript.

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Acronyms and Abbreviations

ABA	American Beverage Association
AHRQ	Agency for Healthcare Research and Quality
AI	artificial intelligence
COI	conflict of interest
CSR	NIH Center for Scientific Review
EPA	Environmental Protection Agency
EPC	AHRQ Evidence-Based Practice Center
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HEI	Health Effects Institute
HHS	Department of Health and Human Services
IARC	International Agency for Cancer Research
ILSI	International Life Sciences Institute
NIH	National Institutes of Health
NTP	National Toxicology Program

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OER	NIH Office of Extramural Research
OSHA	Occupational Safety and Health Administration
PCORI	Patient-Centered Outcomes Research Institute
PFAS	per and polyfluoroalkyl substances
PFOA	perfluorooctanoic acid
UCSF	University of California, San Francisco
USDA	United States Department of Agriculture

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1

Introduction[1]

Governments, philanthropic organizations, and private industry fund human health and medical research. As National Academies reports have noted, different sponsors[2] might influence research so that the results are more favorable to their agents. There are various ways that funders can influence research, such as by affecting the portfolio's scope, specific questions asked, experimental design, and choice of principal investigator (PI) (IOM, 2009, 2011, 2014). It might also bias result reporting, analysis, dissemination, and communication and data availability, reanalysis, and replication. As one publication noted, "Reporting bias can skew the perceived risk–benefit ratio of treatments, mislead medical professionals and policy makers, and ultimately result in suboptimal medical decisions" (Mitra-Majumdar and Kesselheim, 2022).

To explore structures, processes, and principles to ensure high-quality health research independent of sponsors' influence, the National Academies Board on Population Health and Public Health Practice and the Board on Health Sciences Policy hosted a 3-day virtual workshop on December 14–16, 2022 that examined the sources of funding of health research and evidence about whether they influence the quality and outcomes of

[1] The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the National Academies, and they should not be construed as reflecting any group consensus.

[2] Throughout this proceedings, funder and sponsor are used interchangeably.

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research. The workshop also discussed models, process, and principles used to protect the independence and quality of research. Box 1-1 provides the Statement of Task for the workshop. The workshop was jointly funded by the Gordon and Betty Moore Foundation and the Rita Allen Foundation.

This Proceedings of a Workshop summarizes the presentations and discussions. The speakers, panelists, and participants presented a broad range of views and ideas. Chapter 2 presents an overview of the evidence regarding whether funding organizations influence research, and Chapter 3 provides examples of sponsor influence on health research. Chapter 4 discusses approaches to protect research integrity, and Chapter 5 examines models, processes, and principles used to protect research independence and quality. Appendixes A and B contain the workshop agenda and biographical sketches of the speakers and session moderators, respectively. The speakers' presentations (as PDFs and video files) have been archived online.[3] Appendix C contains the workshop speaker disclosures.

BOX 1-1
Statement of Task

An ad hoc planning committee will plan a 2-day public workshop exploring structures, processes, and principles to ensure high-quality health research independent of the influence of research sponsors, including industry, philanthropy, and government.

Although the focus is on human health research, models and examples of preclinical research funding or non-health-specific research might be included in the discussion. While the focus is on the conduct of research, attention might be paid to the award process and to research agenda setting.

The workshop will examine

- the sources of funding of health research, including during the life cycle of knowledge generation, from original research to reanalysis and replication to clinical and public health information dissemination,
- evidence regarding whether source of funding influences study quality and outcomes, and
- models, processes, and principles used to protect the independence and quality of research.

A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

[3] The workshop speakers' presentations are available at https://www.nationalacademies.org/event/12-14-2022/sponsor-influences-on-the-quality-and-independence-of-health-research-a-workshop#sectionEventMaterials (accessed February 3, 2023).

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Do Sponsoring Organizations Influence Research?[1]

To serve as a foundation for the workshop, Lisa Bero, chief scientist at the Center for Bioethics and Humanities, professor of medicine and public health at the University of Colorado Anschutz Medical Center, and the Cochrane Collaboration's senior editor for research integrity, summarized the evidence on sponsor influence. Research is a cyclical process that involves designing questions and methods, conducting research, and reporting the results, which generates further questions for additional research. If any of these steps fail, the value of the resulting evidence, synthesis, systematic reviews, and health and public health guidelines may be questionable. No aspect of the process should be unduly influenced or biased, she said. Bias is defined as a systematic error, or deviation from the truth, in the results of a study. It can overestimate or underestimate the true effect of an intervention, depending on the research question. It could affect clinical trials on a drug, for example, by producing results and conclusions that overestimate efficacy or underestimate harm.

When studying bias, Bero uses a technique she called "meta-research," which is research on research. As an example, she cited a Cochrane systematic review in which she and her colleagues examined bias in 75 industry-sponsored drug studies. One analysis explored whether the reported statistical significance of drug efficacy estimates differed by sponsor. In other words, are some studies more likely to have statistically

[1] This section is based on the presentation of Lisa Bero, University of Colorado Anschutz Medical Center.

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Highlights[a]

- Industry-sponsored research or author conflicts of interest (COIs) associated with results and conclusions that favor the sponsor are called "funding bias."
- Industry-sponsored studies report statistically significant results and/or larger effect sizes more often than non-industry-sponsored studies.
- Bias can appear at four points in the research process: when the agenda is set and how the question is asked, the method and its internal validity, how the study is conducted, and whether the results are published in full.]

[a]This list is the rapporteurs' summary of points made by Lisa Bero, and the statements have not been endorsed or verified by the National Academies. They are not intended to reflect a consensus among workshop participants.

significant efficacy results, an outcome that would be favorable for the drug's developers, when the developers sponsor the trial? This analysis included 25 papers covering almost 3,000 studies and compared studies with drug industry sponsors with all of those with other sponsors, mostly government and nonprofit organizations. Industry-sponsored studies were about 30 times more likely than non-industry sponsored studies to report statistically significant efficacy estimates (Lundh et al., 2017). Bero pointed out that there was no significant difference in the risk of bias between studies with industry sponsors and other sponsors.

Another study she cited examined whether the effect sizes of nutrition study results differed by sponsor. The investigators looked at the association of dairy intake and cardiovascular disease (Chartres et al., 2020) and found that industry-sponsored studies had a larger effect size, a favorable result for dairy intake. "The non-industry-sponsored studies are almost seeing no effect when we combine them, and the industry-sponsored studies have a larger effect," explained Bero. She added that detecting effect size difference in meta-research studies is difficult because many factors can influence it.

Meta-research studies often examine study conclusions; one of the first meta-research studies looked at whether the conclusions of reviews on secondhand smoke differ by sponsor. Bero and her colleague examined topic, year of publication (to account for the results changing as evidence accumulates), whether or not the review was peer reviewed, and whether the review was sponsored by industry or a different sector. The only factor associated with the conclusions of these reviews was the sponsor. "Tobacco industry-sponsored reviews were almost 90 times more likely to conclude that secondhand smoke was not harmful," said Bero. "That raised some red flags."

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Similarly, another meta-analysis found that industry-sponsored research or author COIs are associated with results and conclusions that favored the sponsor (Chartres et al., 2016). This affects a study's results and the authors' conclusions, said Bero, and is called "funding bias." Bero noted that the results of a study (not the conclusion) are important for conducting systematic reviews and formulating health and public health guidelines. However, conclusions are often picked up by lay media and read by those wanting a quick summary of evidence. She added that meta-research provides answers about an observed bias in results or conclusions, except when all the studies are sponsored by companies that made the drug. Furthermore, meta-research studies demonstrate that funding bias exists but do not explain the mechanisms by which it can occur.

HOW DOES BIAS HAPPEN?[2]

Bero and colleagues (Odierna et al., 2013) wrote about what they called the "cycle of bias" that identifies four points in the research process where bias can appear: when the agenda is set and how the question is asked, the method and its internal validity, how the study is actually conducted, and whether the results are published in full (Odierna et al., 2013). What is published, said Bero, influences additional questions and meta-analyses and systematic reviews.

Methods other than meta-research have been used to study industry influence within the cycle of bias. One approach looks at study protocols or full reports, such as those a sponsor submits to the Food and Drug Administration (FDA) or that are part of human ethics research protocols and compares them to what is published. Another approach is to analyze internal industry documents released through legal settlements, which describe companies' scientific research and publication strategies. This method was used with the tobacco industry and then the pharmaceutical and chemical industries. Examining these documents has provided good insights into what the mechanisms of bias might be, said Bero. Another approach is to interview the researchers and funders to determine how and where bias occurs.

The Research Agenda

One source of bias is when industry sponsorship influences the research agenda, described Bero. She and her colleagues conducted a

[2] This section is based on the presentation of Lisa Bero, University of Colorado Anschutz Medical Center.

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scoping review of all studies that examined the influence of the research agenda by sponsors and found that the agendas rarely align with public health questions or prevention. For example, research on gambling funded by the gambling industry tends to emphasize psychological or genetic characteristics associated with gambling addiction and the genetic predisposition hypothesis. This is similar to the research the tobacco industry conducted that promoted the idea that tobacco addiction was related to genetic factors, not the product itself, said Bero.

She acknowledged that sponsors can fund whatever study they want, but for meta-research or systematic reviews, it is important for the researcher to know that the research sponsor may provide a skewed body of evidence on the research questions and the topic area as well. For example, meta-research on nutrition studies found that food industry–funded studies were more likely to focus on micronutrients or minor components rather than on whole diets or dietary patterns. "You can see how this would have a commercial interest, because then those elements can be manipulated within the products, whereas the companies do not profit directly from whole dietary patterns," said Bero.

One analysis of studies funded by Coca-Cola, for instance, found that it was much more likely to fund research on exercise than on sugar (Fabbri et al., 2018). Another study of research funded by five tobacco companies through the Center for Indoor Air Research identified both peer-reviewed and non-peer-reviewed projects (Barnes and Bero, 1996). The latter, which were not published in the scientific literature, were used in court cases and focused on secondhand smoke. None of the much larger body of peer-reviewed research funded by the center focused on secondhand smoke; rather, it addressed subjects such as whether carpet off-gassing was harmful or having a plant in the office improved indoor air quality. These two examples, said Bero, "show how industry sponsors can drive a research agenda toward what we call 'distracting research,' or research that distracts from harm of their product."

Research Methods

Bero then discussed whether the observed bias identified by meta-research studies can be explained by differences in the methods used by industry and non-industry sponsors. In meta-research studies of drug studies, for example, the methods assessed include whether studies were appropriately blinded or randomized and usually do not differ by sponsor, largely because they are often regulated. However, Bero explained, it is important to examine whether standards (including statistical information) differ by sponsors, given that sponsors have become involved in setting standards. For example, the tobacco industry promoted standards

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that would favorably evaluate and apply to secondhand smoke (Baba et al., 2005). Its approach was to argue for a larger effect estimates (e.g., odds ratio) for harm than for efficacy. "Of course, that ignores all sorts of things about population risk and the level of exposure that is happening," said Bero. She noted that none of this planning was public until litigation led to the tobacco industry releasing internal company documents.

Industry was also heavily involved in crafting the Brussels declaration on ethics and principles for science and society policy making (Kazatchkine et al., 2017). Of the 165 names on the declaration, 26 were affiliated with the tobacco or alcohol industries, and the declaration lined up with an action plan for influencing science policy developed by the tobacco industry 20 years earlier. Release of the Brussels declaration prompted Bero to write an editorial listing 10 tips for spotting industry involvement in science policy (Bero, 2019). The lesson, she said, is to be aware of where the standards are coming from and who develops them.

Conduct of Research

Bias can arise when investigators do not conduct their studies according to the research protocol. Internal pharmaceutical industry documents, said Bero, show that research and scientific publication are part of its marketing strategy, and the goal is to use research to disseminate information widely through the medical literature (Steinman et al., 2006). This strategy makes her worry about whether what is getting published is really research. To control for this possibility, many journals have introduced statements regarding sponsor involvement, but Bero questions whether this guarantees that nothing is going on behind the scenes.

When Bero and her colleagues interviewed the lead academic investigators for 200 industry-funded drug trials, all of which had statements to the effect that the sponsor had no role in study design or conduct, 92, 73, and 87 percent of investigators said the sponsor was involved in study design, data analysis, and reporting the findings, respectively (Rasmussen et al., 2018). In addition, only 33 percent of the 80 authors commented that the author had the final say on what appeared in the publication. "This is a little alarm bell about these statements that we see in papers," said Bero. "It really should not assure us that there is nothing going on behind the scenes in terms of industry involvement in the conduct of these studies."

Publication

Despite many approaches to determine whether studies are published in full, the most stunning information comes from internal company documents, said Bero. One set, for example, showed that a sponsoring

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pharmaceutical company would publish the results only if they showed a statistically significant finding for drug efficacy. When Bero and her collaborators reviewed internal documents and the medical literature, they found that a cluster of studies that produced statistically insignificant results were not published, in contrast with those with statistically significant results for the same drug (Vedula et al., 2009). In addition, they found instances where the pre-specified primary outcome was subsequently replaced with a different outcome which was statistically significant. This, said Bero, is "a big no-no." Of the 19 industry-sponsored trials of gabapentin for neuropathic pain, selective outcomes were published in four papers, selective analysis occurred in 11, and seven were not published at all (publication bias). She noted that detecting this kind of bias when reading a paper is difficult and requires meta-research or comparing publications to protocols.

Though she used drug company examples to illustrate the four elements of the cycle of bias, Bero noted that publication bias is not limited to that industry. A study of internal corporate documents on perfluorinated chemicals that she is conducting with colleagues at the University of California, San Francisco (UCSF) found that industry was late to publish studies documenting the influence of perfluorinated chemicals on human health. Given these chemicals remain in the environment for a long time, that is neglegent, said Bero.

BREAKING THE CYCLE OF BIAS

Bero provided a list of steps that could address the problem of sponsor-associated bias:

- Publicly prioritizing research agendas and funding.
- Recognizing industry funding and COIs as a source of bias and account for it.
- Requiring open data for all published protocols and registered reports.
- Eliminating sponsor-associated bias at a structural level through policy.
- Rethinking funding and COI disclosures.
- Establishing independent publishers of research.

For additional potential solutions, she referred workshop participants to some of her publications on commercial influence in health (Lexchin et al., 2021; Moynihan et al., 2019).

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DISCUSSION

When asked about the importance of nonfinancial factors with regard to COIs, Bero explained that many of the science policy or evaluation tools that industry is driving emphasize these factors and ignore the large body of evidence showing that financial COIs lead to systematic biases in research. For her, papers that emphasize nonfinancial factors in COI statements are a red flag that the industry might be involved (Bero and Grundy, 2016). "Some of it has really gotten just quite ridiculous, when we know there is a large body of evidence showing that financial conflicts of interest influence nutrition research, and to argue that whether somebody is a vegetarian or practices yoga has more influence than [financial COI], there is just no evidence for it," said Bero. She noted that she and a colleague published a paper on managing COIs in guideline development that provided evidence-based guidance on how to rate the level of risk associated with different types of interests (Parker and Bero, 2022).

As for improvements, Bero noted a move to provide more open access to data, particularly on drug trials, and big changes to disclosure policies, but disclosure is not a way to eliminate these biases, only to facilitate studying them. Unfortunately, she said, she has not seen a trend of decreasing industry sponsorship, despite changes in how industry money funnels into a university, which is something to watch.

Session moderator Lonnie King, dean emeritus of the Ohio State University College of Veterinary Medicine, asked Bero if sponsors predetermine that they will have a say in the final publication. Bero replied that what she has seen is sponsors occasionally wanting to look at a paper before it is published and including that in contracts. What researchers are telling her, though, is that funders are coming back and suggesting changes to the contract.

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3

Example of Funder Influence on Health Research

Six speakers presented examples of how sponsors influence health research. David Michaels, professor at the Milken Institute School of Public Health at George Washington University, discussed the rise of corporate disinformation about harms. Adrian Hernandez, vice dean for clinical research at the Duke University School of Medicine, shared his perspective on the multiple entities that can influence research results. Laura Schmidt, professor of health policy in the UCSF School of Medicine, addressed industry funding bias in nutrition science. Martin McKee, professor of European public health at the London School of Hygiene and Tropical Medicine, provided many cases in which important evidence does not get included in research papers and hence is not part of the systematic reviews and meta-analyses that inform policy. Adam Dunn, associate professor of medicine and health at the University of Sydney, discussed how artificial intelligence (AI) can help fill in the blanks that McKee identified. Finally, Dean Schillinger, professor of medicine at UCSF, told a story about American Beverage Association (ABA) influence on diabetes research. Cary Gross, professor of medicine and public health at Yale University, joined the panelists for a discussion moderated by Ross McKinney, chief scientific officer at the Association of American Medical Colleges (AAMC).

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Highlights[a]

- Corporate entities that manufacture doubt and uncertainty in science are a threat to human health. (Michaels)
- Open science, which includes increased transparency and access to data, can help address the risk of explicit and implicit bias. (Hernandez)
- Industry funding biases areas of research and marketing in the field of nutrition, which can lead to public health harm. (Schmidt)
- Publication bias, or selective publication of study findings, can be misleading. There are studies that were conducted but were not published. Without publishing all research, we do not have the full picture. (McKee)
- AI technology, such as natural language processing and machine learning, have the potential to identify publications with outcome reporting bias. (Dunn)
- Industry has unfavorably influenced science in multiple, insidious ways. (Schillinger)

[a]This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies. They are not intended to reflect a consensus among workshop participants.

PROTECTING PUBLIC HEALTH IN THE FACE OF CORPORATE DISINFORMATION[1]

David Michaels noted that it is now standard operating procedure for corporations to create and disseminate disinformation by hiring "product defense" experts to manufacture scientific uncertainty about potential harms caused by their products or activities. Some call this "doubt science," as it creates uncertainty. This practice, said Michaels, traces back to the tobacco industry's strategy to counter the idea that smoking caused illness, which became important once researchers began publishing studies in the early 1950s showing the relationship between cigarette smoking and lung cancer. Hill and Knowlton, a public relations firm, advised the industry on how to manufacture uncertainty to convince people that evidence was insufficient to stop smoking or regulate tobacco. The details of this strategy were revealed in a memo,[2] part of the trove now housed at the Truth Tobacco Industry Documents library at UCSF, stating that "doubt is our product since it is the best means of competing with the

[1] This section is based on the presentation of David Michaels, George Washington University.

[2] Available at https://www.industrydocuments.ucsf.edu/docs/psdw0147 (accessed February 2, 2023).

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'body of fact' that exists in the minds of the general public. It is also a means of establishing a controversy."

Michaels explained that creating controversy and confusion is the basic idea behind many examples of corporate disinformation activities. The tobacco industry, said Michaels, did everything it could to say other factors cause lung cancer and that not everyone who smokes will get lung cancer. It created its own newsletter, *Reports on Tobacco and Health Research*, that it sent to physicians and researchers and featured stories such as "Lung Cancer Rare in Bald Men" and a report on a study that supposedly showed that small babies born to mothers who smoked were less likely to die than those born to nonsmokers.

The fossil fuel industry took the same approach regarding climate change, explained Michaels, and even funded an entire industry of people who look like scientists and claim scientists disagree about climate change. He noted that internal papers from fossil fuel companies revealed they all had a tremendously accurate understanding of what would happen if humanity kept pumping greenhouse gases into the atmosphere. "Yet they also funded these groups that said we do not know enough, there is a lot of controversy, so let us not do anything," he said.

Product Defense Firms: A Growing Industry

Michaels called this new disinformation industry the "Enronization of science"—phony companies producing paperwork and documents that claim something without any evidence to support it. "There are these scientists, many of whom work for very lucrative scientific consulting firms, who have been hired to defend products or activities in the regulatory or legal arenas, and the value of that work is to influence regulation and litigation, not to produce valid science," said Michaels. "In fact, their science is really of questionable value." These firms tell prospective clients they take advantage of the concept of "innocent until proven guilty" that is ingrained in U.S. society. Applying that concept makes people think, without saying so, that the product or activity is presumptively innocent, which is a much higher bar to getting something off the market to protect the public's health, he added.

As an example, Michaels showed a document in which Hill and Knowlton listed case histories detailing its work on selected environmental and occupation health issues. It provided this document to the beryllium industry when it was about to be regulated over danger to human health. One of those case studies described how DuPont hired the firm to calm fears around the allegations that fluorocarbons were depleting the ozone layer, which would increase the risk of skin cancer. That public relations and disinformation campaign delayed regulations for several years,

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which enabled DuPont to sell a new fluorocarbon product and maintain market share. Michaels noted that the scientists who produced the evidence linking fluorocarbons to ozone depletion won the Nobel Prize in Chemistry in 1995 for their work.

In another example, Michaels described how an extensive effort by the Weinberg Group on behalf of two pharmaceutical companies led to a 10-year delay before FDA withdrew its approval of a particular drug as a result of post-approval studies showing the drug caused more harm than benefit. Similarly, diesel engine manufacturers attempted to delay the classification of diesel exhaust as a human carcinogen by impeding epidemiologists at the National Institute of Occupational Safety and Health (NIOSH) and National Cancer Institute (NCI). NIOSH and NCI's studies of lung cancer among miners who worked deep underground mining materials that do not cause lung cancer but alongside giant diesel engines, conclusively demonstrated the link between diesel exhaust exposure and lung cancer (Attfield et al., 2012; Silverman et al., 2012).

When the World Health Organization (WHO) moved to classify diesel engine exhaust as carcinogenic to humans, Michaels explained that the industry hired product defense firms to conduct a disinformation campaign designed to confuse the public and regulators. It relied on legislation designed by the tobacco industry that required any studies done or paid for by the federal government to release their raw data to anyone who wanted to reanalyze the data. Epidemiologists, said Michaels, can take data from a positive study, change the parameters, and turn a positive result into a negative one, which is what the industry consultants did (Chang et al., 2018; Crump et al., 2015, 2016).

In another example Michaels cited, DuPont hired a product defense firm to muddy the waters regarding perfluorinated compounds PFOS and PFOA. In 2002, following the first relevant lawsuits, West Virginia, based on a recommendation from that product defense firm, set safe levels in drinking water at 150 parts per billion, or 150 times DuPont's internal safe level. In 2007, DuPont hired ChemRisk, whose scientists had worked for the tobacco industry, to estimate the risk among populations that drink PFAS-contaminated water, and ChemRisk concluded that exposures were about 10,000-fold less than levels considered to be a health risk by an independent panel of scientists who had recently studied PFOA (Paustenbach et al., 2006).

From 2005 to 2013, independent scientists conducted numerous studies on workers and residents exposed to PFOA and found probable links with ulcerative colitis, thyroid disease, testicular and kidney cancer, pregnancy-induced hypertension, and hypercholesterolemia. However, in 2014, 3M, facing a lawsuit brought by the State of Minnesota because it had contaminated the water around its plants, hired product defense firm

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Exponent to conduct a strategic literature review of the published data. It concluded "the epidemiologic evidence does not support the hypothesis of a causal association between PFOA or PFOS exposure and cancer in humans" (Paustenbach et al., 2006). Nevertheless, 3M settled the lawsuit for $850 million.

Michaels noted that the U.S. National Toxicology Program (NTP) reviewed the evidence in 2016 and concluded that PFOA and PFOS are presumed to be immune hazards to humans. Gradient, another product defense firm, was hired by 3M and said that the hazard ratings for both should be downgraded (Beck, 2017). However, based on a growing number of quality studies, EPA issued a health advisory for both at levels of 70 parts per trillion, and in 2022, EPA revised that advisory, lowering the safe levels of PFOA and PFOS to 0.004 and 0.02 parts per trillion, respectively. "While industry was saying there is not enough compelling evidence that they cause illness, EPA is saying there is no evidence to say these levels are too low," said Michaels.

Who Pays the Price?

Michaels said the people sickened by exposures that should have been prevented pay the price for such obfuscation. Occasionally, shareholders pay a price when their corporations are caught manipulating scientific evidence. Johnson & Johnson, for example, recently stopped selling its iconic talcum powder globally after losing several lawsuits based on studies showing an association between ovarian cancer and using talcum powder contaminated with asbestos.

Michaels disclosed that he was an unpaid witness in one lawsuit brought by 22 women in Missouri with ovarian cancer; he had access to documents revealing the disinformation campaign. "The jurors were given documents showing how [Johnson & Johnson] and trade associations tried to convince the U.S. government not to label products containing talc as potentially carcinogenic," said Michaels. These documents outlined how product defense firms would create a reasonable doubt in the minds of NTP's Board of Scientific Counselors, which was considering categorizing "asbestiform talc" as a human carcinogen and non-asbestiform talc as reasonably anticipated to be a human carcinogen, and cause more confusion over the link between talcum powder use and ovarian cancer. The jurors, after seeing these documents, awarded the women $25 million each plus $4.14 billion in punitive damages, which was later reduced to $2 billion. According to Michaels, one juror told the press, "We were just trying to find something [Johnson & Johnson] would feel."

Johnson & Johnson is facing approximately 38,000 ovarian cancer lawsuits and attempting what Michaels called a "Texas two-step." "They

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want to avoid liability by creating a subsidy that will have all that liability and spinning if off into bankruptcy, which means most of those women will never see anything or very little in a lawsuit,"[3] he said. Michaels pointed out that if Johnson & Johnson had taken its talcum powder off the market in 2000 when it learned about the asbestos and replaced the talc with corn starch, which it has since done, it would have avoided these lawsuits.

The Threat to Public Health

In a book Michaels wrote that discussed these examples, he stated that corporate disinformation threatens human health (Michaels, 2020). Disinformation campaigns have negatively affected the air and water, driven the opioid and obesity epidemics, increased the number of children poisoned by lead in paint and the prevalence of alcohol-related diseases, and even delayed the National Football League from dealing with chronic traumatic encephalopathy resulting from players' blows to the head, said Michaels. In addition, the work of these mercenary scientists hurts the credibility of all scientists.

To counter these disinformation campaigns, Michaels said it will be necessary to learn to distinguish between real and manufactured uncertainty. "We have got to build the scientific evidence base from research produced by independent, unconflicted scientists," he said, citing the Health Effects Institute (HEI),[4] a public-private partnership the supports research on the health effects of air pollution, where the funding is balanced between EPA and the automobile industry, as a positive example of how utilizing industry funding can balance biases. He also called for polluters and producers of hazardous chemicals to pay for but not be able to control the research and recommended moving away from regulating toxic chemicals one by one and instead regulating them as a class. For example, data on all 9,000 or so perfluorinated compounds do not exist, but enough is known about some to make the reasonable assumption that they all could be somewhat hazardous and should be regulated as a class. "The presumption of innocence has to end," said Michaels in closing. "Chemicals are not innocent until proven guilty. We need new solutions, and we have to be bold."

[3] As of January 30, 2023, a federal court ruled that Johnson & Johnson cannot use bankruptcy to resolve litigation over claims its talc products cause cancer https://www.cnn.com/2023/01/30/business/johnson-and-johnson-talc-bankruptcy/index.html (accessed February 21, 2023).

[4] https://www.healtheffects.org/about (accessed April 11, 2023).

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THE INTENDED AND UNINTENDED CONSEQUENCES OF HEALTH TECHNOLOGY AND OBSERVATIONAL REAL-WORLD EVIDENCE[5]

Hernandez provided a perspective on the multiple entities that can influence research results. First, he asked the workshop participants to consider the broader question of who influences research results. Influencers include funders, investigators, and technologies. In fact, he said, all of these can influence research results, making it important to be aware of explicit and implicit bias and the behavioral economics that occurs at both the individual and organizational levels. As for which funders might influence results the most, Hernandez named the life sciences industries, government agencies, contract research organizations, data aggregators, research technology companies, and social networks. When he was vice dean for overseeing clinical research and research integrity, he saw examples of each of these at play.

For instance, Hernandez discussed a case involving a first-of-its-kind clinical trial completed in 2011. This was the largest clinical trial ever, and the investigators presented the results at a major meeting and published their findings in the *New England Journal of Medicine*. The results, he said, were "pretty neutral," with the drug producing mild benefits. As a result, sponsor interest in funding further analyses of the study was low or nonexistent. Still, a colleague advised Hernandez—the young faculty member who was the coordinating center's PI for the trial—to hold on to all the data because he could use them to conduct many analyses and answer many questions, which could make his career and pave the way for funding via multiple mechanisms.

Because the initial sponsor's lack of interest in conducting new studies or analyzing completed studies, the risk for sponsor influence might seem unlikely. However, said Hernandez, future sponsor influence is a risk, is much more difficult to track, predict, or anticipate, and can be large. For example, another company might be interested in that study's clinical area and want to access the unique dataset. Hernandez might have some implicit bias to develop research questions that might align with those of the funder, which could be another biopharmaceutical company or a government agency. He noted that he remembers worrying about doing the right thing, given that many parties were interested in the study's data.

Next, Hernandez pointed out that many published studies cannot be replicated for various reasons, either unintentionally or sometimes intentionally because of implicit bias. In 2011, for example, researchers at

[5] This section is based on the presentation of Adrian Hernandez, Duke University.

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Bayer found that its scientists replicated originals results in only 21 percent of the studies they examined (Prinz et al., 2011); in 2012, researchers at Amgen found that only 11 percent of preclinical cancer studies had replications that could confirm their conclusions (Begley and Ellis, 2012). Possible causes of the reproducibility crisis include fierce competition arising from lower funding levels, higher future stakes for creating intellectual property that could be of value to others, structural problems and hierarchies that prevent openness of research results, and the complexity of science and data providence (Harris, 2017). "Influence can come in many flavors," said Hernandez.

As a second example, he discussed a hypothetical case in which a junior investigator develops a concept to improve functional capacity in cardiopulmonary disease with the potential to turn it into a novel intervention. With intellectual property pending, the investigator develops an experimental plan that includes three series of early-phase studies funded by their academic center via a start-up agreement, with plans for future funding through National Institutes of Health (NIH) K or equivalent or R01 grant mechanisms. Hernandez identified some potential influence to generate positive results and innovative experimental designs, which might come from the institution funding the research, given the potential for commercial interest. He added that a behavioral economics concept called "prospect theory," which highlights issues around loss aversion of future winning, may influence people's decisions (Barberis, 2013).

In another hypothetical, researchers design a novel trial platform that will collect data remotely from participants and harvest electronic health records automatically. It could solve many of the world's problems, by allowing patients anywhere to enroll and enabling researchers to acquire their data seamlessly. Funding for a pilot to evaluate feasibility of going to a decentralized model comes from a nonprofit organization, with a research technology company providing in-kind or highly discounted support. The company is aiming for the trial to generate positive results and has plans for scaling the technology with a series of funding rounds and perhaps a public stock offering. The questions, said Hernandez, are whether the company might influence the results, what the quality of the data will be, and if the data will be available in an open-access venue.

These examples have led Hernandez and his colleagues to formulate a model of the research ecosystem with multiple influencers and stakeholders (see Figure 3-1). "We tried to provide a comprehensive view of this, noting that there are many potential gains from different points of view and there are needs to try to address this in a much more public or open way so that we have trust and transparency," said Hernandez. "If you are part of any of these groups, you probably have been in a situation where there may be either direct or indirect influences or even potentially politi-

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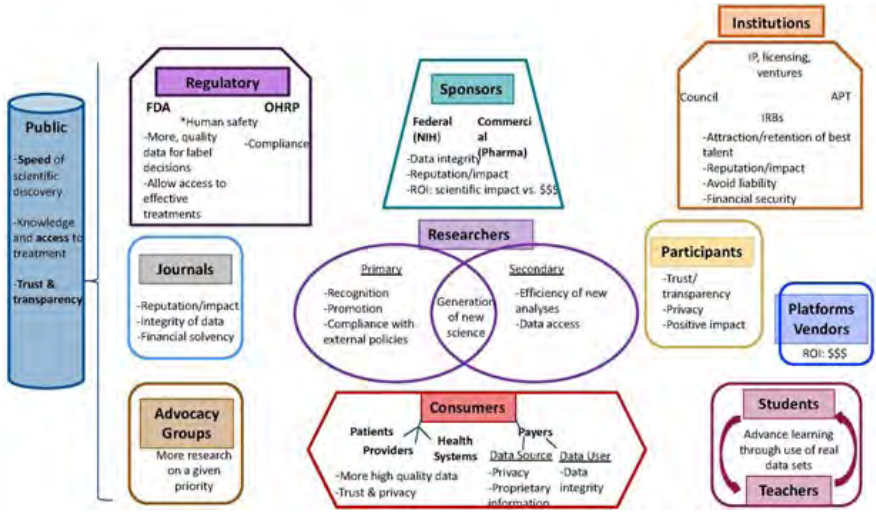

FIGURE 3-1 The influences and stakeholders in the health research ecosystem.
SOURCE: Presented by Adrian Hernandez on December 15, 2022.

cal concerns that come up, and there have been times where unfortunately the political environment can influence what people do."

Hernandez identified different organizations that continue to address these different issues. The American Heart Association and American College of Cardiology, for example, have been trying to ensure that the cardiology community is proactive around issues of professionalism and ethics by identifying four essential components of a COI compliance program: disclosure of interests, assessment of interests, management of interests, and oversight and enforcement of a conflict management plan (Benjamin et al., 2021). He noted that all four are essential, mere disclosure or reporting is not enough, and the mere presence of an interest is not enough to create a COI. Most COIs are manageable if the conflict compliance program is implemented and maintained effectively, and the entire process must be conducted and overseen with complete confidence.

To address potential implicit bias, Hernandez said it is important to ensure awareness of associational or intellectual interests, that future gain may be important, and that the intellectual interest or agenda can drive different decisions on study design and how the investigators report their results (Benjamin et al., 2021). Open science can address this concern, he noted, and the biomedical research enterprise has been making progress around open science, but unpublished results remain that can be unlocked both for gaining insights and to establish trust in the data and research results.

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In summary, Hernandez said influence on research programs and results comes from many directions. Most of the focus has been on funders, given the risk of explicit bias, but implicit bias may exist. Checks and balances are needed, which regulatory agencies often provide to benefit the public. "But we as a community have to consider how we promote open science, whether that is in academia, health care systems, or with other players, to help address this risk of bias, both explicit and implicit," said Hernandez.

When asked about any clues or methodology he would recommend exposing where biases may influence research, Hernandez endorsed increasing transparency around data and allowing access to them. "Just the potential for someone to lay eyes on it is a way to make sure that at least some of the implicit biases may go away," he said. The other aspect is to make sure people understand where other players have influence, such as through in-kind support, and ensure it is disclosed.

INDUSTRY FUNDING BIAS IN NUTRITION SCIENCE ON ULTRAPROCESSED FOODS[6]

When Schmidt began to explore the nutrition science field, she was surprised at how common it is to accept industry funding. Her research focused on ultraprocessed foods, which according to the NOVA classification (Monteiro et al., 2018) are "industrially processed foods that combine refined sugars, fats and salt, and chemical additives." This classification system, she explained, has become an engine for policy change and the international movement to regulate these foods using front-of-packaging warning labels. Countries throughout Latin America are doing that. Efforts also exist to tax such foods, particularly sodas and sugar-sweetened beverages.

Industry sponsors of ultraprocessed food research are large transnational corporations (see Figure 3-2), said Schmidt. Her argument for considering the connection with COIs in research is that these are the alcohol or tobacco of the food system. "Yes, there is conflicting science around whether broccoli is good for you or if nuts are good for you, but ultraprocessed foods have this footprint of public health harm and that raises the stakes in getting the story right scientifically about how they are affecting health," said Schmidt.

Ultraprocessed foods are abundant. In the United States, for example, 57.9 percent of calories consumed come from them (Martínez Steele et al., 2016), and observational studies link them to obesity, Type 2 diabe-

[6] This section is based on the presentation of Laura Schmidt, University of California, San Francisco.

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FIGURE 3-2 Industry sponsors of ultraprocessed food research.
SOURCE: Presented by Laura Schmidt on December 15, 2022 (Oxfam International, 2013).

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tes, hypertension, heart disease, and some cancers. Clinical trials have shown that a diet of them increases energy intake by some 500 calories a day (Hall et al., 2019) and can be habit forming, with almost 70 percent of them being "hyperpalatable," or industrially engineered to trigger the dopaminergic reward system (Fazzino et al., 2021)

Most meta-studies on funding bias in food research focus on ultra-processed foods. Some of these analyses have identified a funding bias: those with industry sponsors were 32.7 times more likely in one analysis (Schillinger et al., 2016) and 57.3 times more likely in another (Litman et al., 2018) to find no increased risk of diabetes from sugar-sweetened beverage consumption. "The industry funding bias in this particular area of nutrition science is quite stunning," said Schmidt.

One well-documented case of sponsor influence examined research conducted by the Coca-Cola Company–funded nutritional research between 2008 and 2016. These studies reported that physical inactivity, not food or diet, is causing the obesity pandemic. Despite good evidence showing that physical activity matters for maintaining weight loss, less evidence exists regarding weight gain. A systematic review found 389 Coca-Cola–sponsored studies in 169 journals, most of which concluded that the obesity crises resulted from physical inactivity (Serôdio et al., 2018). When the *New York Times* published an article with the headline, "Coca-Cola Funds Scientists Who Shift Blame for Obesity Away From Bad Diets" (O'Connor, 2015). To address the critique, Coca-Cola established a "transparency initiative" that listed all the studies it was funding on its website. However, a secondary analysis found that Coca-Cola only reported about 5 percent of the studies it funded (Serôdio et al., 2018).

One reason nutrition science and ultraprocessed food research may be a special case in terms of COI is that historically, most nutrition research is industry funded. One study estimated that the federal government in 2009 funded approximately $1.5 billion compared to $60 billion from the food industry (Mozaffarian and Forouhi, 2018). The synergistic relationship between academics in nutrition and agriculture research and the food and beverage industry traces back to U.S. land grant institutions, said Schmidt. Even to this day, academics and industry funders have a tight relationship, particularly in agricultural research. Another reason is that research priorities vary between NIH and the U.S. Department of Agriculture (USDA) in this country and between the Food and Agriculture Organization and WHO internationally. Much of the U.S. nutrition science research funding comes from USDA, where agricultural and food industry interests are high priorities, said Schmidt. "There is no National Institute on Nutrition, so public funding in this space is much tighter than in other areas of medical research," she added. In addition, many industries have a stake in nutrition research, including agriculture,

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chemical, agrochemical, fossil fuel, pharmaceutical, and even tobacco. She noted that tobacco companies are involved through their food subsidiaries (Nguyen et al., 2019, 2020).

The scientific paradigm for nutrition research informs a root issue in funding, said Schmidt. The dominant paradigm, known as "nutritionism," focuses research on the health benefits or harms of a single food or nutrient (Scrinis, 2013). This approach is a holdover from a field focused historically on vitamin deficiencies and global undernutrition. The problem, said Schmidt, is that whole diets matter more for health today than single nutrients. It also gives rise to "food fads" that demonize sugar, fat, or salt; this shifting advice confuses the public, which undermines the credibility of nutrition science. However, nutritionism and the single-nutrient idea are critical tools for the food industry (Nestle, 2002). "There is a real concern around these single-nutrient studies that are used as an industry marketing strategy to either tout the health benefits of their products or make the case that they are not harmful," said Schmidt.

She said that an issue in ultraprocessed food research is that the industry is positioned to influence the research agenda and narrative for nutrition science. One reason for this is that industry sponsors most U.S.-based professional societies and journals in the field (see Table 3-1). For example, the International Life Sciences Institute, which Schmidt said is a well-researched front group for food and beverage industry interests,

TABLE 3-1 Industry Sponsors of Nutrition Science Organizations and Scientific Journals

Professional Organization	Sponsored Journals	Selected Corporate Sponsors
American Society of Nutrition	Journal of Nutrition American Journal of Clinical Nutrition Advances in Nutrition Current Developments in Nutrition	Danone General Mills Mars Mondelez Nestle The Sugar Association
Academy of Nutrition and Dietetics	Journal of the Academy of Nutrition & Dietetics	Abbott National Confectioners Association Quaker Wyman's of Maine General Mills
The Obesity Society	Obesity	Nova Nordisk Lilly Pacira Biosciences

SOURCE: Derived from Schmidt presentation slide 17.

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funds the Oxford Academic *Nutrition Reviews*. "Here is the case where the entire journal is being driven by an industry front group," said Schmidt.

Schmidt concluded with recommendations for addressing some of the issues she raised:

- Increasing government and philanthropic funding to better balance the funding arena so that investigators can rely less on industry funding.
- Pushing back on nutritionism by funding research on whole diets and foods based on the level of processing.
- Applying more scrutiny to COIs in ultraprocessed food research given the health harms associated with them.
- Earmarking revenue earned from soda and fat taxes to fund independent research on ultraprocessed foods.
- Creating a central public repository of information on scientists' COI statements, perhaps following the model of clinicatrials.gov, so that journalists and members of the public can better understand who is giving them nutrition information.

WHAT YOU DO NOT SEE IS WHAT COUNTS: A PEEK BEHIND THE SMOKESCREEN[7]

McKee described work conducted when he was the unpaid editor in chief of the *European Journal of Public Health* (1998–2003). He noted that much of the evidence policy makers use comes from systematic reviews and meta-analyses and that well-established checklists exist for testing the validity of the studies that go into these. The difficulty with those checklists, he said, is that they only prompt the reviewer to assess what is in a paper and not go beyond that, making it difficult to see the whole picture.

In an ideal world, said McKee, a systematic review will capture all the studies that researchers have published, which will balance out the uncertainty relative to effect size of smaller studies with the results from larger studies. An asymmetry between smaller and larger studies is a clue that studies are missing. The problem arises when this distribution is less random than it may seem because researchers are less likely to publish smaller studies. A good example comes from the history of the tobacco industry suppressing results showing that exposure to secondhand smoke is harmful. He pointed out that despite growing evidence of a demand for smoke-free environments as early as 1979, the public had little confidence that the tobacco industry was interested in its welfare. Industry's official

[7]This section is based on the presentation of Martin McKee, London School of Hygiene and Tropical Medicine.

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position at the time was that epidemiological research cannot prove a causal link between exposure to tobacco smoke and disease, particularly for passive smoking, where industry argued the apparent increase in health risks was too small to provide any confidence in the findings.

However, said McKee, industry was secretly funding epidemiologists, who often did not know it, and got them to agree to a code of good practice that advises discounting a relative risk of less than 2. Conveniently, said McKee, the relative risk typically found in studies of passive smoking available at the time was about 1.3. Industry also promoted the idea that even if studies demonstrate an effect, it was most likely attributable to confounding factors, as those people who live with smokers differ from those who do not in many ways, such as diet. Industry also claimed no biological evidence showed that secondhand smoke causes disease: "We within the industry are ignorant of any relationship between smoking and disease. Within our laboratories no work is being conducted on biological systems" (Ciresi et al., 1999).

McKee got involved because, as a journal editor, he had overseen publication of a confounder study on the characteristics of women married to smokers and nonsmokers. Nothing was wrong with the unexciting paper, but after publishing it, McKee was told that the Dr. Rylander had undisclosed links to the tobacco industry. "He denied it, and a very lengthy correspondence followed. At the same time, he sued two antitobacco advocates in Geneva for libel," said McKee.

When informed of this possible link, McKee did some digging through the trove of tobacco litigation documents at UCSF and found evidence of transferring significant sums of money. McKee found that this researcher acted as a link between a testing plant in Germany and the Philip Morris headquarters in Richmond, VA (Diethelm et al., 2005) and also organized symposiums to convey the message to researchers and to the public that "…the available data on the harmful effects of smoke on nonsmokers was insufficient and inconclusive, notably in view of other factors susceptible of influencing their health." That quote, said McKee, came from a court hearing for the libel case he mentioned, for which he and others were witnesses.

Dr. Rylander also worked with a Kansas law firm known to be at the center of the campaign to distort the evidence on passive smoking. One memo from it stated, "Dr. Rylander prepared a brief memorandum for internal use only concerning a workshop. His major point was that he did not feel that the workshop could or would be in a position to give environmental tobacco smoke a 'clean bill of health.' However, Dr. Rylander did believe that he could bring a healthy skepticism to the conference and some of the claims being made about environmental tobacco smoke." The Swiss court ruled against Rylander, with the court judgment noting that

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on at least one occasion, he had altered his results after conferring with Philip Morris.

McKee referenced a 1968 document in which a Philip Morris vice president expressed concern that industry was depending on monitoring the literature to alert it to research from studies "oriented to seeking out and highlighting the negatives associated with tobacco smoker." Dr. Rylander argued that the industry needed to obtain its own facts and data to avoid being surprised by information from outside sources and "to be able to interpret and understand the results of such studies."

Philip Morris was not the first tobacco company to conduct its own biological research. American Tobacco had done so and "relocated [it] under conditions of extreme secrecy… to new research facilities." Its chief executive officer had reservations about the wisdom of these studies, but he agreed that the research should take place in Europe, which "presents an opportunity that is relatively lacking in risk and unattractive repercussions in this country."

In 1970, Philip Morris purchased a German testing institute to research other causes of smoking-related diseases to "get the industry off the hook." However, rather than buy the institute itself, it funneled the purchase through the Fabrique de Tabac Réunies, based in Neuchâtel, Switzerland, to conceal its involvement. Despite no formal connection with the testing institute, Philip Morris would authorize any study proposals, and the connection was so well hidden that hardly anyone at Philip Morris knew about it. According to 1996 testimony from a former Philip Morris employee, "All in all, it seemed as if there was an inner company within Philip Morris that conducted at least some of its investigations behind the scenes on a strict need-to-know basis. Interestingly, many if not all these activities appeared to be related in one way or another to these sensitive topics of smoking and health."

When McKee and his colleagues gained access to the tobacco industry documents, they found over 800 studies on sidestream smoke—the smoke from the lighted end of a burning tobacco product—conducted between 1981 and 1989. The testing institute had 53 publications, only 16 percent of which mentioned tobacco and related terms even though over 95 percent of the work was for Philip Morris or Fabrique de Tabac Réunies. However, between 1990 and 1998, 63 percent of the publications concerned tobacco; in 1990, Philip Morris was advised that the testing institute's work could no longer be assumed to be safe from disclosure.

The papers the testing institute published, said McKee, focused on research on other possible causes of lung cancer, such as green tea, to cast doubt on the value of cotinine—a chemical formed when the body metabolizes nicotine—as a marker of exposure to environmental tobacco smoke, and research purporting to show that cigarette additives are harmless. A

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few papers came out suggesting that tobacco might be harmful, though McKee felt this might have been an attempt to restore credibility. Over 100 animal studies showing that sidestream smoke was often more toxic that what a smoker would inhale were not published yet served to manipulate experimental conditions to produce more desirable results and commission independent researchers at arm's length for studies whose results were preordained.

McKee's point was that it is not just the research one can see that is important. "The importance of this is that often we are told that we should set aside all these other considerations and we should simply look at the quality of the science and the paper in front of us. We should not be concerned about who funded it. We should assess it on the basis of the methodology and the results that are presented. I would argue that this is very naïve because it is what we cannot see that is important," said McKee.

CAN DATA AND AI MAKE IT EASIER TO MANAGE THE IMPACTS OF COIS?[8]

Dunn focused on a potential solution for managing the influence of research sponsorship and financial COIs in more sophisticated ways that go beyond retrospective analyses that discover problems after the harm has been done. He noted the distinction in meta-research between funding for research and financial COIs that represent money or other financial gain for being an expert. Dunn also reiterated statements by previous speakers that influence happens when studies are funded, designed, and reported and that sponsor influence can also happen in systematic reviews, guidelines, what the media products, and what the public consumes.

One of the earliest studies his team conducted in this space examined systematic reviews regarding two drugs used to treat influenza, Tamiflu and Relenza. When the reviews had financial COIs or received funding from the companies that produced Tamiflu or Relenza, they were more likely to reach favorable conclusions regarding using the drugs in broader populations. "Unsurprisingly but also importantly, systematic review authors are also able to manipulate and change the design of their reviews to reach conclusions that are favorable based on their agendas," said Dunn. His takeaway is that the research agenda can shape every part of the design, reporting, synthesis, and dissemination of health research.

In a study with Quinn Gundy, who spoke on the final day of the workshop, Dunn went through the disclosure of COI and funding statements for a random sample of articles published in journals that had signed onto

[8] This section is based on the presentation of Adam Dunn, University of Sydney.

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the International Committee of Medical Journal Editors' expectation on disclosures. They discovered that 23 and 64 percent, respectively, included positive and negative conflict of interest disclosures, and 14 percent did not have a disclosure statement[9] (Grundy et al., 2018). and the percentage with disclosures was higher (over 31 percent) for drug studies and commentaries of any type. Another finding was that articles with COIs were more likely to be published in high-impact journals and receive media attention, suggesting that people are disproportionately exposed to research at higher risk of presenting biased results, conclusions, and opinions.

Influence is hard to catch, said Dunn. He explained that when applying the standard tools to measure risk of what is published, the things measured are very similar, but the difference in results and conclusions remain. "Put simply," said Dunn, "there are hidden factors that lead to favorable conclusions in studies that are sponsored by industry. This means that it is not easy to identify or quantify the influence on design and reporting of studies using standard tools." Meta-research is one approach to identify and measure influence, but these studies require substantial detective work by experts going through many sources of information, many of which require time or effort to access. As a result, no obvious way exists to investigate the trustworthiness of every single study, review, or media communication associated with health research. "It ends up being just too much work," said Dunn.

Dunn explained that disclosure is not enough; even with perfect disclosure practices, the reader is left with having to decide whether to ignore it, minimize it, be wary of the results, or trust the research more because they can assume that the authors must be experts to have access to industry funding. He argued for better and more accessible records of sponsorship and financial COIs among the people who produce and report on research. This would enable automatically labeling research protocols, registrations, reports, reviews, and media communications with better indicators of how much weight to give to those results and conclusions or to indicate that the study is likely to be so compromised it should not be considered in syntheses. Dunn said that calls for author-centric public records of COIs go back to at least 2007 (Rubenfeld, 2007), and he made the same argument in 2016 (Dunn, 2016).

Modern AI, and natural language processing in particular, may make meta-analyses easier but also cause the biases discussed at the work-

[9] "Disclosures were classified as positive when at least 1 author reported a conflict of interest of any type, excluding current study funding or industry employment; negative if all authors stated they had no conflicts; and missing if there was no disclosure statement." (Grundy et al., 2018).

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shop to manifest in ways that traditional meta-research methods may not detect. For example, depending on how a question is phrased, an AI chatbot might correctly summarize study results or put a marketing spin on it. The problem is that the evidence the AI draws on cannot be determined. "We can be reasonably sure that it is not assessing the evidence for bias or for reliability, it is not looking at financial COI, and it may be assuming that if the majority of studies are favorable, then that must be the truth," said Dunn.

On the other hand, he added, it may be possible to develop natural language processing methods and tools to automatically extract and compare information to support meta-research studies investigating factors that might indicate bias. These include comparing design factors in protocols and registrations, such as changes in primary outcomes or the choice of comparators or identifying missing links between registrations and the articles reporting their results (Bashir et al., 2019; Liu et al., 2022; Surian et al., 2021). AI tools might be able to automatically extract structured summary data from places such as clinicaltrials.gov to compare with what is reported to detect outcome reporting bias. Ultimately, said Dunn, the goal would be to bypass the reporting in articles altogether and have AI synthesize the results directly from structured results data and flag a paper as risky, adjust the weight given to it in syntheses, or discount it completely. AI may also be able to determine whether summaries prepared for a general audience are fair or biased representations of what the paper reports and concludes (Harrison et al., 2020; Shah et al., 2019).

Dunn called for serious consideration for implementing and properly funding three things that can have a transformative effect on how evidence is used and represented in policy, practice, and the public domain. The first is to establish an author-centric open registry for funding and COI data that is not restricted to physicians in single countries or held within institutions. It should connect the ORCID and CrossRef digital identifiers. Second, the methods used to analyze bias in meta-research should be standardized so meta-research studies can be further aggregated. "This is not to say that meta-researchers are bad at sharing data, because they are quite good at it, but rather that we can do more," said Dunn. Third, taking both of those actions would enable researchers to do a better job building machine learning methods for estimating the likelihood that a registration, report, review article, or media communication presents a distorted view. This would allow for flagging a paper for further investigation or finding ways to reduce its influence on policy and practice, said Dunn.

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SPONSOR INFLUENCE IN DIABETES RESEARCH: AN INDUSTRY CASE STUDY[10]

Schillinger explained that the diabetes epidemic affected over 400 million people globally in 2015 and is projected to affect approximately 8 percent of the entire global population by 2040. "The rate of the rise of the diabetes epidemic has been inexorable," said Schillinger. However, he added, a public health turnaround may be happening in the United States, and it is likely connected to a decline in longer-term trends in consumption of sugar-sweetened beverages, which peaked around 1998, thanks to changes in social norms related to research findings around the negative health impacts. He noted that diabetes prevalence has been following the longer-term trends in that consumption, with a delay of approximately 15 years. "This may represent the beginnings of a very important public health turnaround that would be very critical to harness and leverage to a greater degree in the United States and, of course, in the global context as well," said Schillinger.

The first part of the case study he presented focused on a court case in which ABA sued the City and County of San Francisco after they passed a 2014 ordinance that would require billboards advertising sugar-sweetened beverages on public grounds—billboards are rented from the city and county—to post this message: "WARNING: Drinking these beverages can contribute to obesity, diabetes and tooth decay." The ABA was suing on constitutional grounds, claiming that the ordinance infringed on its "commercial free speech" by compelling manufacturers to include warnings that were scientifically controversial, misleading, and untrue. Schillinger was a scientific expert witness; he then wrote a short paper describing how both science and public health had been put on trial (Schillinger and Jacobson, 2016) and ABA attempted to use the tools of science to cast doubt on that causal relationship.

Schillinger reminded participants that science attempts to combine unbiased experimentation with objective observations of the natural world to accumulate knowledge that can help approximate truth. "We can never really determine truth through science; we can only get closer and closer to what we believe is the truth," he said. "In that regard, this case revolved entirely around science and the nature of truth."

In the hearing for the case and the expert reports submitted by industry, the focus was on the scientific veracity of the warning. The city, backed by his report, responded that it is factually true and strong science supported these causal relationships. Industry argued that it was uncon-

[10] This section is based on the presentation of Dean Schillinger, University of California, San Francisco.

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stitutional for their commercial free speech to be infringed or chilled by having to include compelled noncommercial speech as a warning, particularly when this speech is "misleading, false or a subject of scientific controversy." Industry cited numerous scientific studies to support its claims of controversy and that the relationship with disease is false.

The district court judge for the case issued an opinion stating that "compelled disclosure must convey a fact rather than an opinion… generally speaking, it must be accurate" and noted that the factual requirement should not "be so easily manipulated that it would effectively bar any compelled disclosure by the government, particularly where public health and safety are at issue" and "controversy cannot automatically be deemed created any time there is a disagreement about the science behind a warning because science is almost always debatable at some level." The judge decided that the warning likely passed the factual and accurate requirement. San Francisco won the case, but that decision was overturned on appeal.

The second part of the case study focused on financial and nonfinancial COIs and provides a cautionary tale about the importance of recognizing the difference between the two. Schillinger explained that when conducting research to prepare his expert opinion, he explored the degree to which industry was behind the controversy in the literature regarding whether sugar-sweetened beverages are causal factors in the obesity and diabetes epidemics. He and his colleagues systematically reviewed randomized controlled trials with outcomes related to markers of diabetes and obesity and systematic reviews and meta-analyses. They identified 60 studies over 15 years, 28 experimental and 32 systematic reviews or meta-analyses. "We asked the question to what extent are funding of the studies or financial support for the authors of studies associated with the outcomes of these studies," said Schillinger.

They discovered that the beverage industry appeared to be heavily influencing scientific findings: 26 articles found no associations between the product and the disease outcomes, and 34 described positive associations (Schillinger et al., 2016). Of the 26 negative studies, 25 had funding ties to the industry; conversely, only one of 34 positive studies had industry ties. The relative risk with respect to finding that the industry had funded a study showing no association, when compared to independently funded studies, was 32.7, similar to what Bero found when she measured the effects of tobacco industry funding on study outcomes. "We concluded that this industry appears to be manipulating the contemporary scientific process to create controversy and advance their business interests at the expense of the public's health," said Schillinger.

This study garnered significant press coverage, and the industry responded with a letter to the editor written by the chief science and

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regulatory officer of the ABA that the *Annals of Internal Medicine* published several months later (Jack, 2017): "Dismissing industry-sponsored research on the basis of funding is no more valid than discarding studies funded by private foundations or groups that advocate for particular policy views. Transparent disclosure of financial COIs and of potential biases, as well as objective assessment of the research according to accepted scientific principles, is the proper approach to adequately vet the strengths of a study." The letter added that, "The authors [Schillinger et al.] should ask themselves whether they are totally committed to their point of view and unwilling to consider other perspectives. Intellectually motivated biases are as important as financial conflicts of interest."

Schillinger argued that treating intellectual and financial COIs as equal is dangerous and seems calculated to undermine the work of independent clinician investigators whose primary obligation is the health of their patients and communities. Accusing investigators concerned about industry influence of intellectual COIs goes back to the 970s and 1980s and was a strategy of the tobacco industry, he explained (Brandt, 2012).

The third piece of this case study, said Schillinger, deals with an attempt by the sweetened beverage industry to influence policy and dietary guidelines. In early 2017, a widely read paper in the *Annals of Internal Medicine* called into question the quality of the evidence used to develop national and global guidelines on dietary sugar intake and cautioned public health officials to be aware of these limitations when considering whether to promulgate such recommendations (Erickson et al., 2017). The primary funding source for this study was the Technical Committee on Dietary Carbohydrates of the North American branch of the International Life Sciences Institute (ILSI), an organization funded by a large number of fast food and junk food industries. As one example, ILSI has been behind studies to make the case that physical inactivity, not food or diet, is the cause of the obesity pandemic.

The *Annals of Internal Medicine* editors asked Schillinger to write an editorial to accompany that ILSI-funded study (Schillinger and Kearns, 2017). Schillinger and his coauthor mentioned that the study had been funded by a trade group that represented the several major food and beverage companies. In essence, they said, that study suggests that placing limits on junk food is based on junk science, a conclusion favorable to the food and beverage industry. They pointed out, however, that the disclosure of the study's funder was not enough to critically appraise it, so they examined the methods used in the review of added sugar guidelines and concluded that "concerns about the funding source and methods of the review preclude us from accepting its conclusions that recommendations to limit added sugar consumption to less than 10 percent are not trustworthy. Policymakers, when confronted with claims that sugar

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guidelines are based on 'junk science,' should consider whether junk food was the source."

According to Schillinger, the industry-funded review suffered from four fatal methodological flaws. The first was that authors used the inconsistency of international and national recommendations across time and across guidelines as a rationale to raise concern about the quality of these guidelines. "However, these guidelines were issued between 1995 and 2016, and one would expect recommendations spanning more than two decades to evolve," he explained. In fact, he noted, recent guidelines from Public Health England, WHO, and USDA showed remarkable consistency; only the 2002 Institute of Medicine guidelines, partially funded by ILSI were the outlier.

The second flaw was that the ILSI-funded review stated that the funding sources for the *Dietary Guidelines for Americans* were unclear, so it questioned their editorial independence and gave it a poor score. This assessment was curious because the review's appendix acknowledged that the guidelines were developed with federal funding and the advisory committee members were vetted thoroughly for COIs per federal advisory committee rules.

The third problem was that the ILSI-funded report used the Appraisal of Guidelines for Research and Evaluation instrument to assess the quality of the guidelines (Brouwers et al., 2010). Schillinger explained that this was inappropriate and essentially guaranteed that the national and international public health guidelines would be given poor ratings. He said that the tool "is designed to assess *clinical practice* guidelines in the treatment of diseases at an individual patient level [and not] the quality and appropriateness of dietary guidelines to assess risks of consumption at the population level so as to inform public health policy." Using this tool, the authors downgraded the trustworthiness of the guidelines because ways to limit sugar intake "were not clearly presented" and "likely barriers to and facilitators of implementation" were not discussed. They also created an overall guideline quality score of 1 to 7, with interrater differences of three points permitted, yet did not report its reliability, said Schillinger.

Schillinger's final critique of the review's methodology was that the authors used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to evaluate the quality of evidence (Terracciano et al., 2010). The authors, said Schillinger, falsely claimed that the food pattern modeling and national caloric data used to inform the U.S. Dietary Guidelines were not publicly available, which prohibited them from applying GRADE, yielding another poor score. Still, they claimed that "using the GRADE approach, we found that the overall quality of evidence to support recommendations was low to very low." This was puzzling, Schillinger explained, because the authors ignored that the

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methods used to assess dietary patterns were extensively described in an appendix, along with a 500-page supporting report.

This case study took a strange turn, Schillinger said, when the *Atlantic* published a cover story on the sugar controversy titled "The Limits of Sugar Guidelines: Is There a Danger in Governments Offering Too-Specific Advice on Sugar Consumption?" It described the controversy raised by the original paper and Schillinger's accompanying editorial and called out Schillinger and his coauthor as part-time advocates against sugar who write articles for Sugar Science,[11] a group described as devoted to educating the public about sugar's health dangers. It also quoted the editor of the *Annals of Internal Medicine*: "It's shown me that COIs are not only financial but also intellectual." In essence, said Schillinger, the editor of *Annals of Internal Medicine* used the same argument that the ABA representative used to undermine his systematic review and current editorial because he had a so-called intellectual COI equal in importance to a financial COI.

That raised the question of whether writing for Sugar Science represents an intellectual COI. Sugar Science, Schillinger explained, is an educational website founded by Schmidt and sponsored by UCSF; it is a repository of studies that address questions about the relationship between added sugar and disease outcomes. It is an academic and educational resource, with no industry funding. He added that he had written one blog post for the website.

Schillinger ended with a list of closing thoughts and questions:

- Industry has unfavorably influenced science in multiple, insidious ways.
- The beverage industry has demonstrated its ability to manipulate the scientific process to shape what is considered scientific "fact" or scientifically "controversial."
- Scientific—and policy making—communities must continue to be vigilant, in defense of pursuing truth for public health, about the effects of financial COIs.
- Many prestigious journals require expert reviews by biostatisticians. Should journals require not only COI disclosures but also careful reviews by experts in COIs?
- Should journal editors' performance be assessed regarding their track record on COIs?
- How can researchers prevent the construct of so-called intellectual COIs from being used to undermine public health? A consortium of

[11] https://sugarscience.ucsf.edu/ (accessed February 3, 2023).

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journals has already made this decision with respect to the tobacco industry.
- When is it appropriate for journals to take a stance against publishing science funded by industries with an established history of manipulating the scientific process to promote their bottom lines while they undermine public health?
- How can researchers educate the media about the potential effects of COIs on science while also promoting public trust in science?

DISCUSSION

Cary Gross joined the session's speakers and noted that one of his first research endeavors was to conduct an umbrella review of the association between financial ties and research outcomes. That review found that the odds of an industry-funded trial yielding a positive or pro-industry outcome were more than three times the odds of a non-industry trial, something that has become more pronounced over the past 20 years. "The impact of industry funding on the clinical research enterprise has been insidious yet transformational," said Gross.

In his field, oncology, published randomized trials conducted by industry have increased from approximately 50 percent of those in high-profile medical journals to almost 90 percent by some estimates. Biomedicine, he said, has reached the point where industry sponsorship of clinical research has become the norm and researchers have become overly reliant on it. "It is causing us not only to have a bias in the research that is being done, but our whole research ecosystem is so dominated by industry sponsorship that it also affects not only the selection of research questions but also the scope and objectives of clinical research," said Gross. He noted that the prevalence of industry sponsorship affects the research not being done, such as comparing two drugs within the same class or two treatment regimens that may be commonly used to determine which one is better. Research in the cancer world is also scant on prevention and on how to identify value-based, equitable, or high-quality care.

As a comment before opening the discussion to the rest of the panel, Gross said that it is important to think through how to best reassess the research ecosystem. "If we were going to design [it] from scratch, we never would have designed it to where we are right now, so how can we think about bold changes to reconfigure our ecosystem so it is meeting the needs of patients and of society?" he asked.

McKinney pointed out that clinical research is expensive, and the federal government has not provided enough funds to counterbalance industry funding of clinical trials. "In fact," said McKinney, "we count on [FDA] to serve as an ex post facto sorter of what is too biased to use as evi-

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dence, and that is probably not enough." He noted that intellectual COI can indubitably be real and meaningful. The question is how to interpret it relative to the weight that comes from having someone design a study with a purpose, which happens with much of the sponsored research that is the subject of this workshop.

Bero noted the many influences on research and that it would be naïve to think that research is not influenced and is value free. What is important, she said, is bias, and the important feature of bias is that it results in a systematic deviation in results and potentially in inferences. "The talks today clearly illustrated these biases related to industry funding," she said.

Bero asked Dunn if an automated tool to identify bias and assess risk of bias in an individual study would include funding source and investigator COI. Dunn replied that as financial COIs are associated with systematic biases, that would be put into a model of risk of bias. Other factors related to personal research agendas would not be included. If he were using machine learning to look for bias, he would capture as much information as he could that would connect to the document, such as the registration, protocol, and text of studies on similar topics, and use examples with bias annotated to train the model.

McKinney noted that the risk of a machine learning model being based on intrinsically biased data is enormous. Dunn agreed and explained that modern machine learning does address factors such as fairness and equity, interpretability, and explainability and other aspects related to generalizability and transportability. A modern model can explain the decision it made, identify the factors it used, and factor in fairness and equity via the technical approach to introduce annotation sampling. This point relates to the need to better share computable data and annotations. "I would love to have a database that has thousands of examples of individual studies that were annotated for bias retrospectively, because I could take those and then apply them to new studies that I had not seen before," said Dunn.

Michaels remarked that it is a given that disclosure is necessary, but one important area does not require disclosure: comments on federal regulations. He noted that the Administrative Procedures act requires all federal agencies to ask for public comment on any new proposed regulation, but a stakeholder who comments is not required to provide any information about who funded the comment. When he was the administrator of the Occupational Safety and Health Administration (OSHA), he included a request for COI disclosure for the proposed standards on worker silica and beryllium exposure. "It was incredibly controversial," he said. "I received a letter signed by 13 Republican senators saying that will discourage people from sending in comments if they have to say who

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paid for it." Fortunately, he said, a strong editorial in *Nature* supported that proposal, and the disclosure requirement remained in place until the Trump administration ended it. "We should know who paid for these comments," said Michaels.

Rita Redberg, professor of Medicine at USCF and chief editor of *JAMA Internal Medicine*, agreed and pointed out that many patient advocacy groups are industry funded, and when she was chair of the Medicare Coverage Committee, many comments would come from representatives from these groups. However, these individuals rarely disclosed that connection, even when specifically asked about a COI. She also said that industry-funded commenters often note nonfinancial COIs to deflect from their financial COIs.

McKinney, posing a question from a virtual participant, asked if the panel could discuss allegiance bias among researchers. He explained that in his area of nutrition research, he can correctly presuppose the direction of an outcome and whether the study is about health risks from carbohydrates, fats, red meat, or other factors based on the title of a paper and the name of a senior author. McKee said that he has seen a great deal of this during the COVID-19 pandemic, where the authors of systematic reviews had a particular view on how serious the virus was that came out strongly in their papers. "One's allegiance to a political party might be correlated pretty well with your allegiance to ivermectin as a treatment, for example," added McKinney, adding that a great deal of evidence shows this was true.

Schillinger said he believes that every paper should be viewed with a concern for bias, but labeling every scientist who has an informed opinion on a scientific matter as guilty of an intellectual COI is a slippery slope. In terms of allegiance bias, he believes that that relationship between an investigator and the public differs greatly from that relationship when it is mediated by a third party whose interests go beyond speaking truth to the public. "This notion of a third party being involved whose interests may supersede those of the public's interest or the pursuit of the truth is the critical difference between one's allegiance to one's identity and identity politics and how that might affect your relationship to the public versus one's relationship to that third party and that third party's mission," Schillinger explained.

Bero cautioned that it is important to distinguish between someone who is an expert in a subject and therefore likely to be able to predict the results of a study from the investigator's lab—which some might construe as bias, as seen with attitudes toward experts during the pandemic—versus someone whose research is biased because of a sponsor's influence on the research. This is the beauty of meta-research, Bero said, because it looks across a whole body of findings on a particular topic and not just

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from a particular lab. "That is when we can detect bias at the systematic deviation in the results when we look across the whole body," she said.

Schillinger asked Dunn what he thinks should happen in terms of publication and dissemination to the scientific community and the public when an AI-generated score suggests bias may be possible. Dunn replied that the first step is to be more transparent about the data, the information underneath the data, and how an experiment was designed. "That is why things such as registrations, protocols, and structured reporting of results are so important, because then we can start to deal with some of the mechanisms of introducing bias into the research," said Dunn.

In addition, with an estimate of the risk of bias in an individual report or media communication, it would be possible to flag it to signal the reader they should be careful about the conclusions they draw and perhaps qualitatively adjust what is known about that study. "I do not have the statistical skills to be able to figure out how we are going to do that," said Dunn, "but there must be some way in synthesis that we can say we expect across this body of evidence that we are going to see more positive results than the truth, and so we need to adjust that."

Gross asked the panelists for ideas on how to engage the media so reporters better understand, report, and potentially mitigate the effect of financial conflicts. Schmidt cited a structural issue: reporters are trained to show both sides and feel compelled to do so even when the evidence base is flawed and biased. In her experience, they have talked about being confused by hearing conflicting scientific opinions. A centralized resource on scientific COIs is needed that allows reporters to know whom they are talking to, said Schmidt. Bero noted that journalist Jeanne Lenzer keeps a long list of researchers without financial COIs for which researchers can apply to be included.[12]

[12] Available at https://jeannelenzer.com/list-independent-experts (accessed February 2, 2023).

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4

Protection of Research Integrity

The session on research integrity featured three speakers. Patricia Valdez, health science policy analyst at NIH and extramural research integrity officer in the NIH Office of Extramural Research (OER), spoke about NIH's extramural research portfolio. Daniel Greenbaum, president of Health Effects Institute (HEI), discussed how to gain sponsor support while maintaining independence. Clive Green, executive director of biopharmaceuticals research and development at AstraZeneca, addressed the application of corporate ethical policies and governance processes with an emphasis on bioethics. The session concluded with a panel discussion

Highlights[a]

- To protect the independence of research and promote transparency, NIH made grant awards contingent on particular policies, processes, and procedures. (Valdez)
- HEI's transparent strategic planning produces policy-relevant science without taking a policy position. (Greenbaum)
- AstraZeneca funds and conducts scientific research but uses bioethics to maintain clinical research integrity. (Green)

[a] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies. They are not intended to reflect a consensus among workshop participants.

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moderated by Aaron Kesselheim, professor of medicine at Harvard Medical School and faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital, in which the three speakers were joined by Nicholas Chartres, director of science and policy for the Program on Reproductive Health and the Environment (PRHE) at UCSF, and Gary Ruskin, executive director and cofounder of U.S. Right to Know.

RESEARCH INTEGRITY IN EXTRAMURAL RESEARCH AT NIH[1]

Valdez discussed NIH steps to reduce bias, in either selecting projects for funding or conducting research. She began by talking about rigor and transparency in grant applications; NIH defines rigor as "the strict application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation, and reporting of results."

In 2016, NIH implemented a policy called "enhancing reproducibility through rigor and transparency" to respond to concerns about the lack of reproducibility of preclinical data in publications.[2] It required grant applicants to describe their research in more detail and how they planned to produce rigorous research. The policy also allowed grant reviewers to judge applications based on the rigor of prior research and plans to address weaknesses in it; the rigor of the proposed research; the role of relevant biological variables, such as sex, on the proposed research; and authentication of key biological or chemical resources (see Figure 4-1). The new policy, Valdez explained, requires applicants to describe how they will achieve robust and unbiased results given the design of their experiments and the methods they plan to use. They also must provide information about the calculations and analyses they plan to conduct.

Avoiding Bias in Funding Decisions

Once a grant application comes into the NIH Center for Scientific Review (CSR), it is assigned to a study section, where the PI's peers will evaluate it for scientific merit, Valdez explained. After the reviewers score the application, the grant goes to the relevant NIH Institute or Center's advisory committee. This step, she noted, acts as an additional safeguard to ensure that it is making the correct funding decision. Next, NIH evaluates the proposal's relevance and need before making the final funding decision and initiating a grant. NIH monitors the grant's programmatic

[1] This section is based on the presentation of Patricia Valdez, National Institutes of Health.

[2] Additional information is available at https://grants.nih.gov/policy/reproducibility/index.htm (accessed February 3, 2023).

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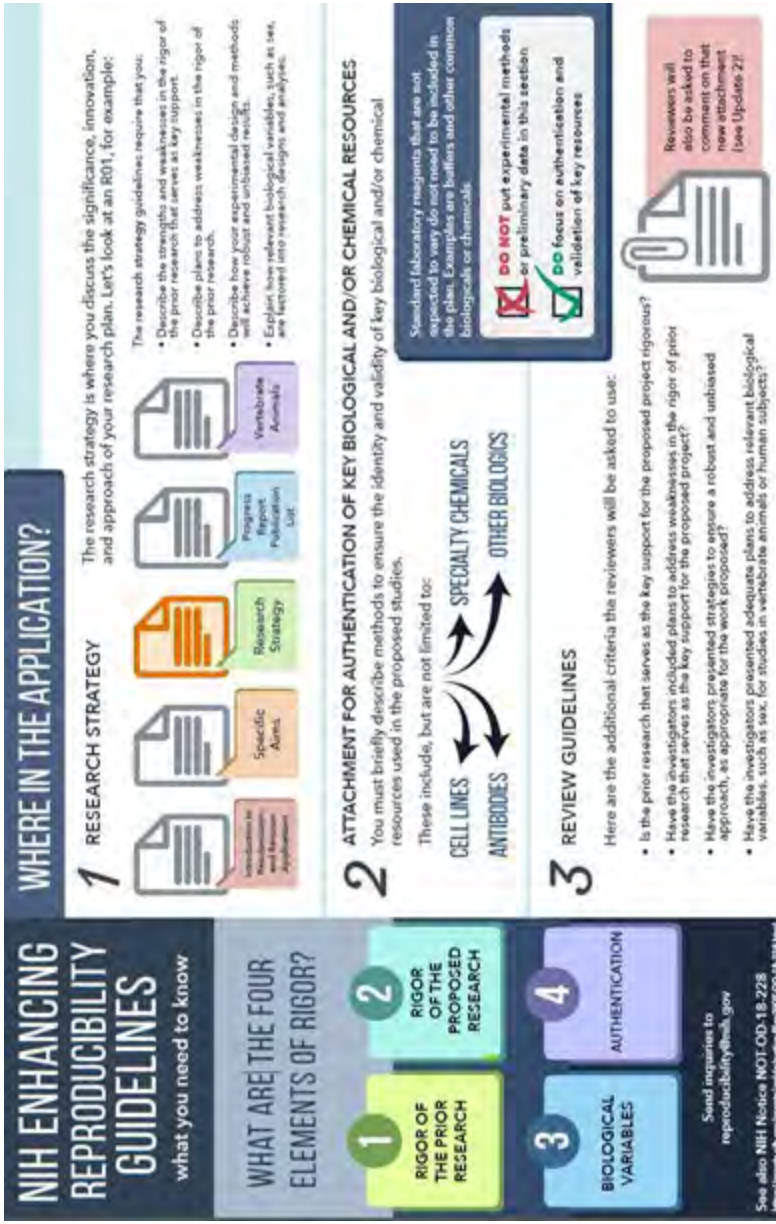
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1 RIGOR OF THE PRIOR RESEARCH
2 RIGOR OF THE PROPOSED RESEARCH
3 BIOLOGICAL VARIABLES
4 AUTHENTICATION
Send inquiries to reproducibility@nih.gov
See also NIH Notice NOT-OD-18-228
WHERE IN THE APPLICATION?
1 RESEARCH STRATEGY
The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let's look at an R01, for example:
Introduction for Resubmission and Renewal Applications
Specific Aims
Research Strategy
Progress Report Publication List
Vertebrate Animals
The research strategy guidelines require that you:
• Describe the strengths and weaknesses in the rigor of the prior research that serves as key support.
• Describe plans to address weaknesses in the rigor of the prior research.
• Describe how your experimental design and methods will achieve robust and unbiased results.
• Explain how relevant biological variables, such as sex, are factored into research designs and analyses.
2 ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES
You must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.
These include, but are not limited to:
CELL LINES
ANTIBODIES
SPECIALTY CHEMICALS
OTHER BIOLOGICS
Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.
DO NOT put experimental methods or preliminary data in this section.
DO focus on authentication and validation of key resources
3 REVIEW GUIDELINES
Here are the additional criteria the reviewers will be asked to use:
• Is the prior research that serves as the key support for the proposed project rigorous?
• Have the investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project?
• Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
• Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
Reviewers will also be asked to comment on that new attachment (see Update 2)!

FIGURE 4-1 NIH infographic illustrating the key features of the new requirements for grant applicants based on the enhancing reproducibility through rigor and transparency policy.
SOURCE: Presented by Patricia Valdez on December 14, 2022 (Swan et al., 2019).

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and business management performance using yearly progress reports that include information on how the applicant is ensuring robust and unbiased research.

Valdez said NIH holds dear several core values for peer review: expert assessment, transparency, impartiality, fairness, confidentiality, security, integrity, and efficiency. Impartiality refers to the management of COIs or the appearance of COIs, and reviewers must certify their COI statements both before and after a study section meets. NIH does not allow lobbyists to serve on study sections. In addition, NIH separates staff functions, so the person overseeing the conduct of research is not the same one who manages the review process. There is also an appeal process if an individual has concerns that the peer-review process was biased.

In terms of the integrity of the peer-review process, NIH staff receives training on how to handle allegations of research misconduct, said Valdez. Before each meeting, NIH instructs reviewers and council members to report an allegation to the designated federal officer, who then reports it to the assigned research integrity officer in the relevant institute or center. NIH may defer the application from review until the Department of Health and Human Services (HHS) Office of Research Integrity (ORI) has assessed the allegations. In addition to the peer-review process, allegations can come from outside NIH, such as the investigator's institution.

Valdez noted that her office handles other integrity-related concerns, such as harassment, bullying, and discrimination, and issues with foreign interference and individuals trying to breach the integrity of the peer-review system. Allegations of grant fraud are sent to the NIH Office of Management Assessment for potential referral to the Office of the Inspector General.

Depending on the outcome of the allegation assessment by ORI and the pertinent institute or center, NIH may contact the investigator's institution, remove an individual from serving on a peer-review committee, refer the allegation to the agency or office with oversight, or take administrative actions. In severe cases, NIH can take regulatory actions against institutions. Given a risk to a grant's funds, the research, or human or animal participants, NIH can take interim actions, such as requiring additional supervision of the individual involved or certification of data, requesting a new PI, restricting funds, or even suspending or terminating an award. NIH may also refer a case or individual to the HHS Office of the Inspector General.

NIH's financial COI policy is based on HHS regulation 42 CFR part 50 subpart F, which addresses promoting objectivity and establishes standards that provide a reasonable expectation that the design, conduct, or reporting of NIH research will be free from bias resulting from any investigators' financial COIs. It requires investigators to report their financial

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interests to their recipient institution, which determines whether a potential COI with the NIH work exists. If so, the institution will provide NIH with a management plan that NIH will either approve or reject.

Clinical Trial Registration and Reporting

Several years ago, said Valdez, NIH began requiring investigators to register all NIH-funded clinical trials at the ClinicalTrials.gov website within 21 days of enrolling the first participant and report a summary of the results within 1 year of the primary completion date.[3] This is required regardless of the study phase or type of intervention, and it is subject to regulation. The policy requires a plan in the grant application that outlines compliance with the policy, which becomes part of the terms and conditions for an award. Valdez said that if an institution does not follow this plan, NIH can terminate an award and even take regulatory actions against an institution. In addition, all clinical trial consent forms must include a statement informing the potential participant about the information posted at ClinicalTrials.gov.

Valdez concluded with a brief discussion on NIH's scientific data-sharing policy, which went into effect in January 2023. It took years to develop, and the idea behind it is that results, both positive and negative, produced using taxpayer funds should be available freely. "This is something that we thought long and hard about, and we are working with the extramural community to make sure that we do have proper plans in place and proper places for storing that data," said Valdez. "We think this will be a very positive step going forward."

When asked which of the methods of oversight she thinks are most relevant to protecting the independence of research, Valdez replied that the two-pronged peer-review process helps ensure that NIH is funding applications based on assessments by their peers. One thing her office sees more of is individuals citing NIH funding in their publications when it does not exist. They do this to get that paper indexed in PubMed, which provides legitimacy.

GAINING SPONSOR SUPPORT WHILE MAINTAINING SCIENTIFIC INDEPENDENCE[4]

HEI, said Daniel Greenbaum, was launched in 1980 after the Environmental Protection Agency (EPA) administrator and motor vehicle indus-

[3] Additional information is available at https://grants.nih.gov/policy/clinical-trials/reporting/index.htm (accessed February 3, 2023).

[4] This section is based on the presentation of Daniel Greenbaum, Health Effects Institute.

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try chief executive officers agreed that an independent entity should produce the science on the health effects of vehicle emissions, which 1977 amendments to the Clean Air Act required. Greenbaum noted that while HEI's sponsors provide input, along with scientific and environmental communities, into the priority topics HEI should address, sponsors have no role in selecting teams to conduct the research, overseeing its implementation, and reviewing its results before publication. Sponsors of HEI's core air pollution programs come equally from EPA and the motor vehicle industry, and HEI has also built partnerships with WHO, Asian Development Bank, the U.S. Federal Highway Administration, and other industries.

HEI has an independent board that the EPA administrator and core industry sponsors approve. Without EPA and core industry sponsor approval, the board appoints two key committees: research and peer review. HEI's commitment to transparency means it publishes all the results of the studies it funds, both positive and negative, along with a detailed commentary by the review committee. It also makes all its data accessible to others and does not take policy positions based on its work.

HEI has funded over 350 studies on a wide range of air pollutants, which have included research on exposure, toxicology, and epidemiology. HEI also conducts detailed reviews of the literature and has a global health program funded by foundations and multinational agencies conducting research and science communication in China, India, Africa, and other low- and middle-income countries. Recently, HEI started an energy program examining the potential exposures and health effects of unconventional oil and gas development (fracking).

Greenbaum explained that HEI produces and communicates trusted science through strategic planning and rigorous competition to produce quality policy-relevant science; being broadly transparent with study methods, results, and data; and not advocating for policies. The HEI strategic plan prepared every 5 years with input from its sponsors, the scientific community, environmental organizations, and others, provides a detailed plan for what should be happening to anticipate future policy and technology events and produce the science that can inform those events. He noted that the plan does evolve. For example, the current plan, produced in 2019 and 2020, did not include a research plan for air pollution and its relationship to COVID-19. Today, HEI has several such studies up and running.

The strategic plan informs a detailed process that Greenbaum said is similar in some ways to the NIH process Valdez described, involving soliciting grant applications, conducting a two-stage review, and overseeing the resulting research. Scientists populate the research committee, and HEI requires them to file COI disclosures and that no members of

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the research committee work at EPA or the core industry funders. Once a project is selected for funding, it undergoes detailed oversight and quality assurance auditing and then must complete a comprehensive report of the findings that goes to the separate review committee. The review committee had no role in the study and implements an intensive peer-review process that includes outside reviewers. The review committee summarizes and communicates the findings through widely available HEI publications, social media, PubMed, and other channels.

Transparency, said Greenbaum, comes about in two ways. First, every PI is free to publish the results of their project in scientific journals, either before or after the internal review process, without HEI input. Investigators must also produce a comprehensive final report of all analyses. The report enables the review committee to understand both positive and negative findings and decide on appropriate ways to interpret the science and inform critical policy decisions. In addition, HEI expects investigators to make the data available publicly. Sometimes, HEI has funded the online publication of complete datasets that other investigators have used for additional studies.

Greenbaum explained that HEI does not take policy positions because of the concern that any subsequent research it might fund would be viewed as supporting that position. Because of this stance, HEI has been asked occasionally to reanalyze policy-relevant data independently. For example, in the late 1990s, EPA was considering a new standard for fine particulate air pollution based on the Harvard Six Cities Study results and an American Cancer Society study. EPA, industry, and Congress called for a reanalysis of the data, and the investigators from the two studies provided full access to their data. After conducting an independent reanalysis, HEI confirmed that the work was of the highest integrity and confirmed the original conclusions.

In another case, HEI funded a study to answer important questions about the cardiovascular effects of exposure to ozone. It involved nearly 90 older adults exposed to ambient and higher ozone levels using a carefully defined protocol (Frampton et al., 2017; Rich et al., 2020). It reported few effects on cardiovascular health but confirmed that ozone has respiratory effects in older adults, and EPA still uses these results to inform its decision making.

At the urging of its sponsors, HEI competitively selected three teams to examine the associations of exposure to deficient levels of fine particulate air pollution in 68 million Americans (Dominici et al., 2022), 8 million Canadians (Brauer et al., 2022), and 25 million Europeans (Brunekreef et al., 2021). These three studies provided evidence of associations with adverse health effects, said Greenbaum. He added that results are at the center of the decision-making process in the United States and Europe

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around exposure to the setting of ambient air quality standards for fine particulate matter.

Greenbaum briefly mentioned that in the early 1980s, Congress funded the HEI asbestos research program. Schools were removing asbestos, with controversy about whether it should be removed from commercial and residential buildings. An independent expert panel reviewed the science and recommended strong steps to minimize asbestos exposure (HEI, 1991).

Greenbaum said that controversy and distrust between major parties helped to create HEI, a public–private leveraged partnership for research investment. HEI was designed for maximum impartiality and credibility, with sponsor input into priorities but no involvement in study selection, oversight, or review. HEI's activities are guided by a carefully drawn, responsive strategic research plan renewed every 5 years as an opportunity to refresh and refocus its research. This approach has resulted in nearly 400 research studies, reanalyses, and systematic literature reviews widely cited in the literature and policy and regulatory deliberations.

Greenbaum noted occasions where regulators have quoted part but not all of a study's conclusions and industry advocates will select the conclusions that are most favorable to them but leave out the accompanying caveats and comments. When that happens, HEI writes to the parties to clarify what it is and is not saying.

APPLICATION OF CORPORATE ETHICAL POLICIES AND GOVERNANCE PROCESSES, WITH A FOCUS ON BIOETHICS[5]

The focus on research integrity at AstraZeneca, said Green, is through the lens of bioethics, which is the practical application of ethics to a range of issues that arise from the study and practice of biological and medical science. Bioethics, he continued, is where AstraZeneca aims to build trust by demonstrating integrity, transparency, and fair treatment in everything the company does. Ethics and transparency, he added, is one of the three pillars of sustainability for the company, along with access to health care and environmental protection.

Bioethics at AstraZeneca is governed under the company's global bioethics policy that covers a range of subjects, including clinical research integrity. Green noted that as a pharmaceutical company, AstraZeneca funds and conducts scientific research, and this policy covers sponsor influence in research that spans clinical and drug discovery activities. Some of the key principles in the bioethics policy regarding clinical research include the following:

[5] This section is based on the presentation of Clive Green, AstraZeneca U.K.

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- Maintain a portfolio of research and development projects designed to deliver effective, safe, differentiated medicines and address unmet patient needs.
- Conduct clinical studies per all regulatory requirements and recognized international quality and safety standards in all countries where the company operates.
- Make information publicly available about the registration and results of the company's clinical trials for all products in all phases.
- Give those participating in the company's clinical studies full, truthful, and understandable information and asking for their consent to be part of the study.
- Conduct preclinical studies to ensure that all safety aspects have been evaluated and that assessing potential risks and benefits justify testing a drug in the clinical setting.

Green said the company's policy on transparency is to share its approach on its external website, share bioethics content through the company's sustainability report, and participate in annual external audits. It also includes registering its clinical and observational studies, posting study results on disclosure websites, making a good faith effort to publish results in peer-reviewed journals in a timely manner, and providing transparency in bioethics actions following applicable legislation, regulations, standards, and guidelines.

To ensure compliance with this policy, Green said that bioethics responsibilities underpin the company's overarching science policy, which is one of four pillars of the company's code of ethics that defines its values and behaviors at work. Every employee, he said, participates in mandatory annual training on the code of ethics and research integrity and relevant governance policies and procedures specific to their role. Employees can report any concerns to a manager, human resources, legal department, compliance representative or an independent third-party group acting on the company's behalf.

The company also has an internal bioethics advisory group that advises on implanting global standards, comprises individuals from a wide range of topics, and is supported by leaders from the company's legal, compliance, and corporate affairs departments. It exists to provide advice, support, and guidance to scientists, project teams, and company leaders on bioethical issues, and it engages in horizon scanning to see where scientific, technical, and societal developments will prompt ethical challenges, said Green.

In addition, the company has an external advisory committee comprising leaders from academic and nonprofit organizations to provide access to expertise in pharmaceutical, research, and public health ethics

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and law. The committee serves as a sounding board for proposals and gives advice and recommendations on ethical issues and societal perspectives. Both advisory groups sit outside the subject area governance structure to retain their impartiality. Green noted that the advisory groups do not get involved in the scientific detail of a proposed study unless a conflict with a company policy arises. A review of the decisions about the scientific details of a project is conducted through the company's governance processes.

PANEL DISCUSSION: WHERE ARE THE POINTS OF INFLUENCE ON SCIENTIFIC RESEARCH

Nicholas Chartres and Gary Ruskin reflected on the presentations. Chartres agreed that disclosing COIs is essential to identify and quantify the level of potential influence but does not protect the science from influence. As Bero noted, research synthesis and systematic review are also critical, and the challenge is identifying and quantifying potential influence when conducting systematic reviews that then inform guidelines or risk assessments used to develop recommendations for protecting public health. "If we do not have methods and approaches to identify COIs and industry sponsorship within those primary studies, and we do not attempt to quantify that level of influence, we may have an evidence base that can be skewed in favor of an industry's product if that is the focus of the evaluation of the evidence," said Chartres, adding that identifying and quantifying COIs in primary studies does not mean removing them from systematic reviews or meta-research but rather considering them in assessing a body of evidence.

Ruskin said that U.S. Right to Know focuses its research on the food and chemical industries, where a public–private partnership, such as HEI, is a nonstarter. "We know from our own investigative research on corporate documents that Coca-Cola and the ultraprocessed food industry have designed and executed an elaborate strategy to promote public–private partnerships as one part of their broader efforts to manage and control the public health discussion, to limit public policy options, to co-opt the public sector, and ultimately to defeat the public health community," said Ruskin. "Based on the evidence that we've uncovered regarding these hidden motives of the food and chemical industry, such a public–private partnership around food or chemical research on policy is not likely to be good for public health."

He applauded Green for his presentation on how the corporate world genuinely struggles with these real problems and questions. In his view, this type of corporate behavior should be encouraged, yet he also questioned the effectiveness of corporate self-regulation of research ethics

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because corporations face no penalties for violating their guidelines. "Corporate codes of conduct can be weakened or abrogated at any moment," said Ruskin, "and that is why solutions to these health research ethics problems will come through federal and state law and policy and not corporate self-regulation."

Green remarked that not all industries are the same and that he has had the experience of being invited by other industries to talk about AstraZeneca's model only to have them reject it because they wanted more involvement in research discussions. Greenbaum noted that one group missing from the day's discussions is the scientific journal editorial community, given that most journals do not want to publish negative results, even for well-executed studies. Green agreed about that dearth of negative results, which will hinder future developments, such as powering AI models. He also noted the consequences for individuals who violate corporate codes of conduct and ethical guidelines.

Bero, speaking from her role as an editor for *Cochrane*, took exception to Greenbaum's comment, stating that evidence from several studies shows that bias about negative results "is really submission bias." Interviews with researchers suggests that some of this bias arises from a sponsor pressuring investigators not to submit negative results. She noted, too, that most medical journals now require publication of raw data and datasets in some open-access forum. However, she added, even though the raw data may be available to peer reviewers, many do not look at those data. "Publication is important," said Bero, "but it is a last step in the research cycle, and we need to think about all the biases that can be introduced along the way."

Redberg said that sponsors could play a role in encouraging or allowing the publication of all results, positive or negative. She explained that as a journal editor, she is interested in seeing studies that change practice, and negative results are just as important because they show what should not be done or does not work. Redberg agreed that data sharing is important, but not all journals require it. As an example, she noted how the Oxford Cholesterol Treatment Trialists Collaboration has a large body of evidence from statin trials, which have industry sponsors, but in 20 years, the collaboration has never made those results available because they are industry's data. She called for industry to adopt policies similar to NIH's on data release. Valdez noted that NIH's new policy requiring grantees to share data will enable administrative actions against institutions or grant holders if they fail to publicly make their data available.

Kesselheim asked Chartres and Greenbaum if they have seen any trends in research sponsorship in their fields and to comment on the extent to which current protections for research integrity keep up with those trends. Chartres replied that his institution has industry documents

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showing that since the early 1990s, the tobacco industry has been intentionally trying to undermine and suppress research around the harms of its products. Over the past 10–15 years, more documents have become available showing that multiple industries have used those same strategies. In terms of safeguards, Chartres believes that the scientific and research community needs to better understand that industry influence is happening, which is why he thinks this workshop is critical to informing the public and researchers about the extent of that bias and how it affects it public health and health care decisions.

Journals requiring COI statements are a step in the right direction, said Chartres, citing the Cochrane model regarding disclosure as one that most journals could use. Cochrane reviews cannot be commissioned or funded by any commercial sponsor that may have a vested interest in the findings of the review, and the first author must have no conflicts. He added that moving toward transparent databases is another important step and that the Physician Payments Sunshine Act, which increased transparency regarding pharmaceutical company payments, would be a good model to follow. Although some safeguards have been put in place, he said they are still inadequate given what the industry is doing to bias the research process.

Greenbaum said that a problem in environmental health research is that public funding has decreased, which raises the question of who the funders are. Fortunately, this field has a mechanism—HEI—for private funding to avoid some of the worst excesses of industry influence. But, at the same time, the limited public investment in research poses a challenge to the scientific community in some areas to continue to produce high-integrity, unbiased research.

Bero, commenting on the spectrum of funding in a particular area, cautioned that it is sometimes hard to understand how the sources have changed without doing meta-research. For example, when she looked at nutrition research, many researchers told her that the food industry funds everything, but it "is an important and influential funder, but it was not the major funder in the spaces we were looking at," she explained. In contrast, it is hard to determine who funded a particular drug study because it was reported under the marketing budget and not the research and development budget. "You really need to dig into company reports to find out, and sometimes they are not transparent," which makes it difficult to get a handle on trend data.

Tracey Woodruff, professor of obstetrics, gynecology, and reproductive sciences at UCSF, wondered if NIH, given the importance of research to the public's health, might consider investing in the kind of meta-research that Bero discussed. Valdez responded that some NIH institutes and centers are funding more meta-research. She also noted that spotting

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nondisclosure is challenging, particularly when foreign interference is involved.

Posing a question from the audience, Kesselheim asked Green if the experts on his company's advisory committees are bound by nondisclosure agreements or can speak up about instances where the committees' recommendations are not followed. Green cited an independent avenue for raising concerns in a safe and trusted environment. Ruskin noted that the life of a whistleblower is hard, though the *qui tam* process can be somewhat friendly. "We need to do everything we can to make whistleblowing something that is accepted and supported in our health science culture," said Ruskin.

Kesselheim asked the panelists for their thoughts on whether protections are sufficient to create public trust in institutions and research findings, and, if so, how best to communicate that so people can understand whom and what information to trust. Valdez replied that public trust is important; without it, people will not participate in clinical trials, for example. This is a difficult problem, she said, because of the disinformation issue, so building trust will depend on science education and ensuring that people are aware of what type of research and when they can trust.

Ruskin commented that the current situation is courting a crisis of confidence in the nation's health institutions, given how heavily rooted they are in an evidence base that "may well not be trustworthy because so much of it may well be tainted by corporate influence." Some estimates, he said, attribute nearly 60 percent of medical research funding to industry, and much of that research will be biased toward product defense and overstating product benefit. "Without a clean and uncorrupted evidence base, many people are just not going to trust or listen to scientific studies, public health leaders, medical institutions, regulatory agencies, and other health bodies," said Ruskin. He cited a 2022 Pew Research poll showing that only 29 percent of U.S. adults say they have great confidence in medical scientists and scientists, in general, to act in the public's best interest (Kennedy et al., 2022). Greenbaum added that transparency is critical to public trust.

Bero noted that preliminary data from a general public survey on COIs show that the researchers could not assess how it affects people's trust because they did not understand the COI statements. The bottom line, she said, is that disclosure will not help with trust, so it is necessary to build people's trust in the science and how it is conducted. Being transparent and making research understandable to a lay audience will be the key, which is why she is a fan of evidence synthesis. She noted that people trust Cochrane reviews and rate them highly because impartial experts vet their information.

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Kesselheim asked the panelists for their ideas about the best opportunities to promote research integrity. Ruskin replied that the most important thing is for the message to come from the top: the president, Congress, governors, and state legislatures. "We have to tell the truth to the American people, that our current health evidence base may well not be that reliable and that as a matter of federal and state policy, we are going to do better and build a health evidence base that people can trust and believe in," said Ruskin. "We cannot allow corporate [public relations] and product defense to pass as science anymore." Valdez echoed that, adding that the "top" also includes the leadership of institutions because they can set institutional policies. She suggested that leaders, and not just trainees, should receive instruction on the responsible conduct of research.

Greenbaum commented that the more transparency in research funding, decision mechanisms, and oversight, the more the public is likely to trust it. He noted that unlike Green's company, some companies do not want to be transparent about who is on their panels and advisory committees. "Figuring out how to improve transparency and make it much more consistently applied will be important," said Greenbaum.

Bero agreed with these points about transparency but said the low-hanging fruit is developing structural mechanisms for ensuring independence from the sponsor, something that transparency does not guarantee. "We need to make sure that the research is under the control throughout the entire research cycle by independent investigators and funders," said Bero.

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5

Considering Models, Processes, and Principles to Protect Research Independence and Quality

The final session featured five presentations designed to provide the attendees with suggestions for how to protect research independence and quality. Sunita Sah, associate professor at Cornell University and fellow at the University of Cambridge, discussed some of the psychological processes involved when considering conflicts of interest (COI). Rita Redberg discussed the appropriate role of a sponsor in studies. Quinn Grundy, assistant professor in the Lawrence S. Bloomberg Faculty of Nursing at the University of Toronto, addressed alternative sources of funding for biopharmaceutical research. Vincent Cogliano, deputy director for scientific programs at the California EPA Office of Environmental Health Hazard Assessment, spoke about protecting the scientific integrity[1] of the *International Agency for Research on Cancer (IARC) Monographs*. Finally, Craig Umscheid, director of the Evidence-Based Practice Center Division and senior science advisor at the Agency for Healthcare Research and Quality (AHRQ), discussed ways of addressing conflicted research when synthesizing evidence. Following the presentations, Woodruff and Joel Lexchin, professor emeritus at York University, provided their insights from the presentations and joined the speakers for a discussion moderated by

[1] Scientific integrity refers to scientific research that is free from politically motivated suppression or distortion. See: https://www.whitehouse.gov/wp-content/uploads/2022/01/01-22-Protecting_the_Integrity_of_Government_Science.pdf (accessed April 21, 2023).

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Highlights[a]

- It is not enough to disclose COIs. Clear policies and procedures are needed to eliminate or mitigate COIs and create a culture of "deep professionalism." (Sah)
- Investigators should be independent of the sponsor throughout the study process, including study design, data analysis, and writing. (Redberg)
- Public sector innovation in drug development and biopharmaceutical research prioritizes equity, affordability, access, and transparency compared to industry-funded research. (Grundy)
- The International Agency for Research on Cancer needs to appoint the most knowledgeable experts, and needs to have review committees free of the perception of COI. IARC has designed systems to avoid COI. (Cogliano)
- Risk-of-bias assessments can help identify and mitigate bias resulting from COIs. (Umscheid)

[a]This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies. They are not intended to reflect a consensus among workshop participants.

C. K. Gunsalus, director of the National Center for Principled Leadership and Research Ethics at the University of Illinois Urbana-Champaign.

A DEEP DIVE INTO PROFESSIONALISM: POTENTIAL POLICY APPROACHES TO COIS[2]

Sah noted that several policy solutions for addressing COIs, such as fines, sanctions, education, second opinions, and disclosure, are largely based on inaccurate intuitions regarding the underlying psychological processes (Sah, 2017). As a result, they tend to fail or have unintended consequences. Two possible solutions, she said, are disclosing COIs and cultivating professionalism.

Sah has studied disclosure extensively, particularly regarding the psychological effects on both recipients (people reading the disclosure statement) and disclosers (those who make a disclosure statement), to see where it hurts and where it could help. In fact, disclosure is the most commonly proposed and implemented solution for dealing with COIs across range of industries and sectors. It is popular for recipients, Sah explained, because it can alert them to potential bias and allow them to decide whether to discount the conclusions or recommendations. "Some

[2] This section is based on the presentation of Sunita Sah, Cornell University.

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people love this because it appeals to our principles for transparency and free markets," said Sah.

Her research has found, however, that a disclosure requirement itself does not work well because even when it is written in simple and clear language, people do not know what to do with it, ignore it, or discount it erratically (Rose et al., 2021; Sah, 2019b; Sah et al., 2016). "There is this large variance, which makes sense," said Sah. For recipients to interpret a disclosure, they need to have a mental model of how the COI has biased the recommendations. Then they can discount the recommendations for exactly that amount of bias.

Studies have found that disclosure of funding sources with a COI may make some physicians r less willing to prescribe the drugs in the paper, regardless of the scientific rigor of the study (Kesselheim et al., 2012). Decreased confidence could be an appropriate response to a COI disclosure, said Sah. She noted that even when the reader is confident about the high quality of the advice that a paper may provide, what she calls a "disclosure penalty" remains (Sah and Feiler, 2020).

Sah identified problematic unintended consequences of disclosure. She has found that when a person is under a high cognitive load, they process a disclosure automatically or peripherally, as opposed to deliberating and focusing on what the disclosure actually means; it becomes a cue to the clinician's expertise and increases trust. She has also found even with decreased trust, which is arguably the correct response to COIs, readers will still comply with the recommendations in a paper because of an unwillingness to signal distrust to those who are disclosing.

Disclosure might be attractive to a discloser, as it can relieve the person of guilt for any unfavorable outcomes, Sah said. It can also limit professional liability. At the same time, she and her collaborators have found that disclosure can lead people to reject COIs so they can announce the absence of any COIs (Sah and Loewenstein, 2014). "People are motivated to appear unbiased, and disclosure works best not when it depends on consumers responding effectively but rather when it influences the behavior of the people whom the disclosure is about, encouraging them to improve and reject conflicts of interest," said Sah. In other words, reputational concerns or an aversion to being viewed as corrupt could be driving this effect.

Across several studies, Sah has found that the effect of disclosure on providers depends on the salience of the professional norms and what those norms are. For example, in a financial context, a "self-interest first" norm, which many laypeople believe about the industry, bias increases with disclosure in that it can change and lower the quality of the advice. In the medical context, where the norm is patient first, bias decreases with disclosure (Sah, 2019a).

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The key, said Sah, is how professional norms influence what people think is the right thing to do in a given situation. "Disclosure can improve the quality of advice, but only if the norm is to place clients first, patients first, readers first, the public first. It acts as a reminder to do the right thing," said Sah. "Just reminding people that you have a conflict of interest works in the same way as the conflict-of-interest disclosure." She added that a self-interest first norm can lead to increased bias in the advice, but disclosure can be a signal that reminds advisors to place advisees first and leads them to rein in bias (Sah, 2019a).

The biggest psychological process to overcome, said Sah, is the amazing ability people have to rationalize. "Once we have disclosed, we think we have dealt with our moral obligations with respect to COIs, and rationalization can crowd out more effective solutions than managing COIs," she said. She does not recommend disclosure as a solution to managing COIs unless it leads people to reject conflicted funding themselves and improve the quality of their advice.

The concept of professionalism, said Sah, has evolved into one that describes how one conducts oneself, or, as one pair of scholars defined it, "a set of values and identities that can be mobilized by employers as a form of self-discipline" (Aldridge and Evetts, 2003). Other scholars state that a belief in self-regulation is a key aspect professionalism (Cheney et al., 2010; Hall, 1968), as is the ability to actively manage the conflict between the client and personal interest to favor the client (Nanda, 2003). If professionalism is a self-concept, the question is whether improving integrity and professionalism will lead to rejecting conflicted funding or make matters worse.

This is an important question, said Sah, because people often think they are immune to unwanted influence. Physicians, for example, say they are not influenced by industry incentives, although they might think that other physicians are likely to be. This often self-serving justification, she explained, leads to a lack of ability to predict influence, which is why physicians and other professionals take great offense at the idea that they could be influenced by financial incentive. "Although a strong sense of professionalism might help defend against intentional corruption, it does not mitigate against unintentional or implicit bias that arises from conflicts of interest," said Sah.

She has found that a high self-concept of professionalism often coexists with a shallow notion of the concept. This can lead paradoxically to detrimental outcomes, such as increased unethical behavior and increased vulnerability to COIs (Sah, 2022). Those with a strong sense but shallow understanding of professionalism might be more likely to accept COIs because of their high confidence in their ability to consciously control for any influence, as seen with overeating and smoking. "If we have a

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strong belief in our own ability to regulate, we will not remove the high-calorie foods from our house, or a cigarette packet from our pocket, so we are more likely to lapse and eat more and smoke more than we want," explained Sah.

In addition, once a physician perceives a COI, a high sense of professionalism may reassure them they can ward off influence, so they work less hard to correct for bias, ironically leading to both greater acceptance of COIs and more bias. "There could be this double harm that can arise from professionalism, in that it makes people more vulnerable to view conflicts of interest as acceptable and succumb to the bias from conflicts of interest," said Sah. Because people remain unaware of the bias, they cannot predict it or recognize it in hindsight, she added.

She called for "deep professionalism": recognizing the risks of undue influence and avoiding COIs in the first place (Sah, 2022). Individuals with deep professionalism embrace continued ethical training to help embed principles and display it with repeated ethical behaviors, said Sah. For example, if a hospital policy bans pharmaceutical representatives from interacting with physicians in their hospitals and ends free lunches, physicians who understand deep professionalism will also reject walking across the street for the free lunches that the company now offers in a hotel conference room. Even though the policy does not regulate behavior outside of the hospital, those with deep professionalism will understand and internalize the principles and values of self-regulation and nurture their values repeatedly with active practice (Sah, 2022).

One solution is to integrate both approaches: have clear policies and procedures to eliminate or mitigate COIs and cultivate deep professionalism. For example, institutions could allow receiving conflicted funding, if researchers are separated from decisions involving the source and do not know the funders' identity. Such a policy needs to be implemented before specific situations arise to avoid distortions, said Sah.

She recounted how one hospital created a central fund where industry could contribute and physicians could apply within the institution. The problem was that after funding, the hospital revealed the source and the physician had to write a thank-you note, which degraded the independence of the research. Bero has been at two institutions that tried to implement a pooling mechanism; companies pulled their funding, presumably because their funding would not be recognized and they could no longer have influence. Sah suggested that companies could disclose how much they put toward independent research and treat that as a positive outcome by showing their commitment to transparency.

Sah said that along with open data, preregistration, registered reports, and a grade or rating on the degree of conflict, cultivating deep professionalism could lead to a self-calibrating effect that motivates people to do

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better and produce higher-quality research. "Integrating these approaches, I believe, is the best approach to managing conflicts of interest," she said.

Gunsalus noted that she has recently encountered a generational concern about the concept of professionalism, that it is limiting and imposing old-style views. Sah replied that she can understand that pushback if professionalism dictates work clothes and other aspects of formality, proposing that "we need to get away from professionalism as being a character trait but more as a set of repeated behaviors that demonstrate ethical behavior."

ROLE OF THE SPONSOR OR FUNDER IN RESEARCH STUDIES[3]

Redberg spoke about concerns related to the objectivity and therefore the reliability of the published science that helps to guide professional practice, treatment guidelines, and how physicians care for their patients. The first item on her list of concerns is the text in a paper indicating evidence of the sponsor involvement study execution, such as choosing the clinical trial sites and investigators, or where the sponsor can adjudicate end points or help analyze the data. Often, she said, the end points in studies are not objective —such as death—but are soft and require adjudication. The subjectivity is further blurred, as the definitions of heart attack and stroke are expanding and no longer clear-cut diagnoses. "It makes a difference who is adjudicating the end point and how objective and blinded they are," said Redberg. Another red flag for her is if the sponsor participated in writing a paper, reviewed it before publication, or had to sign off on the final product.

As an example, she cited the COAPT trial of a cardiac device (Stone et al., 2018). Multiple papers had shown that it did not benefit patients, but the company-sponsored trial reported positive results. Upon reading the paper to see what was different compared to all the others, she found that the protocol had been designed by the investigators in conjunction with the sponsor, who also participated in site selection, management, and data analysis. In addition, many of the authors had a significant financial relationship with the sponsor. Still, FDA approved the device, and it is in current practice, all based on this one trial where it seems that the sponsor had a great deal of influence.

Other concerns of Redberg pertain to the outcomes of a study. Industry sponsors prefer to use composite outcomes with soft end points, which makes trials faster and cheaper. Composite outcomes are driven by the weakest (and most commonly occurring) end point. For example, heart

[3] This section is based on the presentation of Rita Redberg, University of California, San Francisco.

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attacks and death are a less frequent but clinically significant outcomes in her field, cardiology, but less frequent than hospitalization or a more subjective symptom, such as unstable angina. She also looks for conclusions that are inconsistent with the results, such as when the conclusions paint negative results in a positive light. In those cases, she always looks for text about the sponsor's role and relationship with the authors. "By emphasizing benefit over harm, there is a risk of misleading clinicians and encouraging use of a device that adds cost and risk without possible benefit," said Redberg.

She recounted an incident involving a researcher at UCSF who conducted a study showing that generic levothyroxine was equivalent to the branded drug Synthroid. They submitted a paper describing the results to a respected journal, but it was pulled at the last minute because the agreement with the industry sponsor gave it final publication approval (it was eventually published). Redberg noted that the University of California has banned contracts that allow funder control of publication, but this is not a policy at all academic institutions.

High-quality sponsor-funded research, said Redberg, requires independent, highly qualified academic investigators. They do not need sponsors to help with putting together and running a trial, data analysis, or writing up the results. She wondered if journals should restrict the sponsor's role in submissions just as papers published in leading medical journals have an absolute clinical trial registration requirement. She noted that *JAMA* had a 2005 policy that any paper with a sponsor involved in the data analysis also had to have an independent statistical analysis, and it is worth exploring if the policy was effective in improving objectivity.

One policy in effect is the requirement to include a data-sharing statement, though most such statements for industry-funded studies say that the investigators are not sharing their data. "I think having data publicly available so that independent researchers could analyze the same dataset would certainly help to improve the objectivity of the science," said Redberg.

The end goal, she said, is that investigators should be independent of the sponsor in all aspects of study design, data analysis, and writing.

ALTERNATIVES TO INDUSTRY: SEEKING INDEPENDENCE IN BIOPHARMACEUTICAL RESEARCH[4]

Grundy noted that private industry, a specific type of institution, share a set of practices as to how they exert influence by sponsoring research. Both economic factors, such as shareholder returns, and politi-

[4] This section is based on the presentation of Quinn Grundy, University of Toronto.

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cal factors, such as the regulatory environment and structure, incentivize those practices. By studying these factors, it might be possible to imagine new conditions for the research ecosystem that address sponsor influence on quality and independence.

Biopharmaceutical companies and medical device manufacturers, as previous speakers noted, are involved in clinical trials in a variety of ways, from providing free study drugs to conducting trials and writing and publishing trial results.

To illustrate the extent to which industry sponsors clinical trials, Grundy cited work that characterized trials initiated between 2006 and 2013 and registered in the WHO Clinical Trials Registry Platform and sorted them by country and World Bank income category (see Figure 5-1) (Atal et al., 2015). Thirty percent had an industry sponsor that was the primary funding source, which Grundy said may underestimate industry involvement. However, looking at the distribution globally and by income category shows that industry sponsors over two-thirds of trials in high- and upper-middle-income countries but only 12 percent in low-income countries. The majority of international trials (80 percent) were industry sponsored.

The talks during the workshop painted a compelling and evocative picture of the web of relationships through which industry can influence research in addition to sponsoring it, said Grundy. She argued that COI is a distinct, though clearly related, concept. It is thus important to understand sponsorship in a social context, which includes the relationships between trialists, researchers, and industry as a backdrop. Given that, Grundy agreed with speakers who articulated and advocated for transparency around these relationships and management strategies that go beyond disclosures, which are visible but not always fit for purpose. "If it is difficult to understand their relevance, we have the likelihood of [disclosure] backfiring," said Grundy. In addition to structured reporting to enable meta-analyses, additional information is needed for disclosures to be relevant, be transparent, and enable accountability.

It is important, said Grundy, not to lose sight of the downstream effects of industry sponsorship, on not only research but health professional education, guideline development, formulary selection, clinical practice, and ultimately the patient. Grundy cited a recent scoping review that mapped the range of medical product industry ties within the health system (see Figure 5-2) and found that most of these activities are unregulated, are opaque, and have real downstream and often harmful effects on patients and other stakeholders in the health care system (Chimonas et al., 2021). "I think it is important to highlight the role of industry sponsorship in research as the root cause of many of these dependencies," said Grundy.

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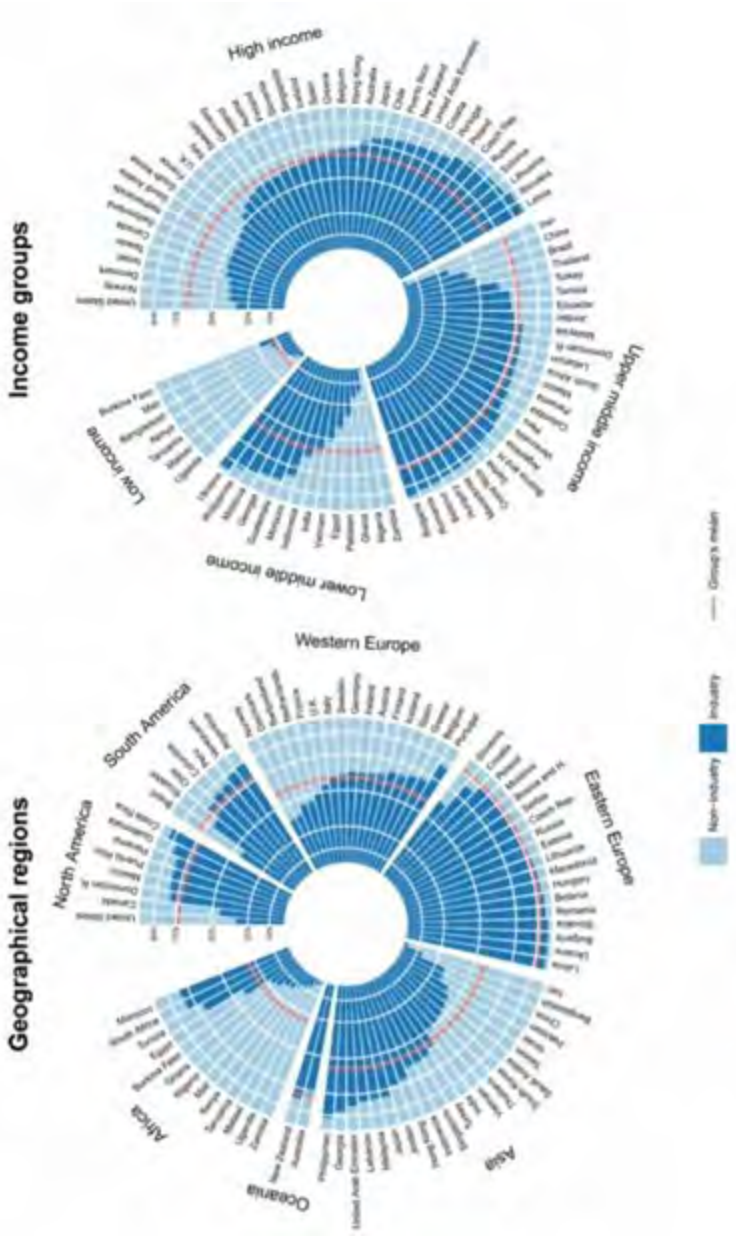

FIGURE 5-1 The dominance of industry sponsors in biomedical clinical trials.
SOURCE: Presented by Quinn Grundy on December 16, 2022 (Atal et al., 2015).

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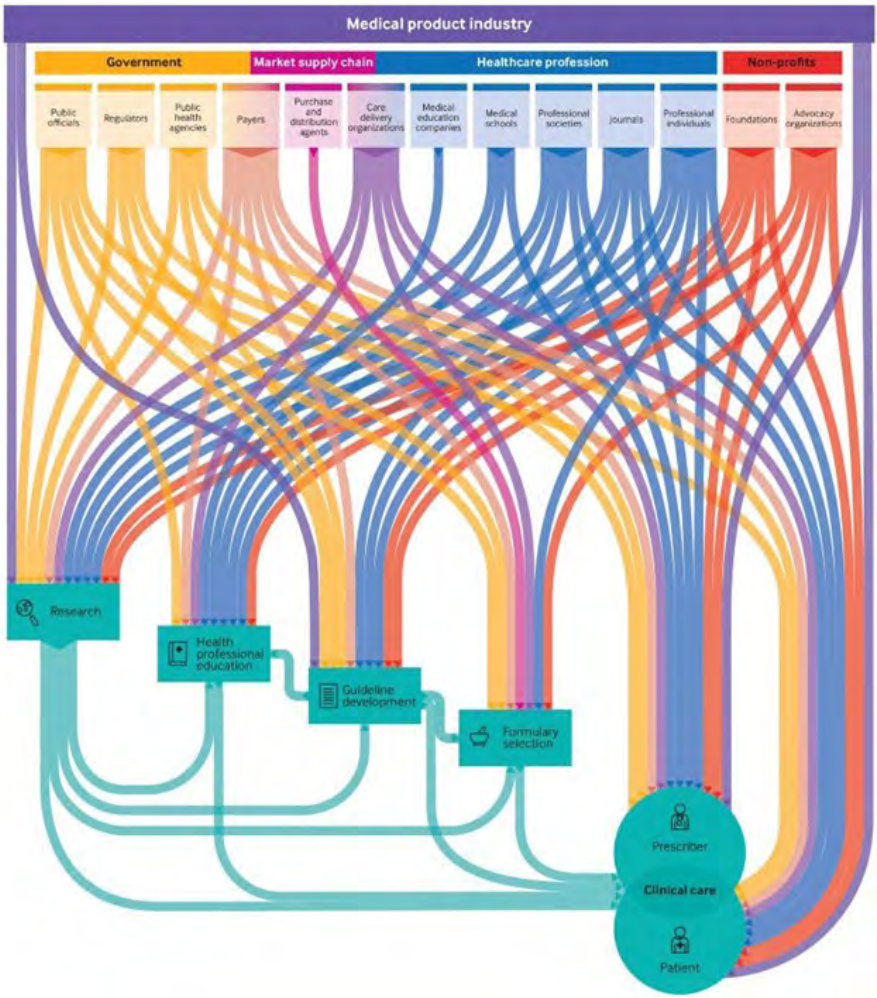

FIGURE 5-2 Mapping medical product industry's ties within the health care system.
SOURCE: Presented by Quinn Grundy on December 16, 2022 (Chimonas et al., 2021).

"Clinicians frequently perceive industry or their representatives as the experts. They rely on industry-sponsored, -conducted, and -curated research and information for clinical practice," Grundy said. Her perspective as a nurse is that this applies to not just drugs or surgical devices, but a range of medical products and devices used in day-to-day care. "Industry is often the only source of information about those products,"

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said Grundy, which means that industry representatives, instead of other clinicians, are taking on the role of educators in terms of integrating information about clinical products into practice. To Grundy, this underscores the need to develop research practices and policies that conceptualize, prioritize, and ensure independence, such as the separation and blinding approach that Sah proposed. Grundy also commented that Sah's notion of deep professionalism is a social practice that requires spaces for training, research, and dissemination.

Grundy was involved in the revision of the 2020 Cochrane Collaboration COI policy and believes this represents an example of a policy lever from a trusted organization to create a norm of separation between those sponsoring research and those appraising, synthesizing, and disseminating evidence in forms that are most useful to clinicians and the public. To her knowledge, the Cochrane Collaboration database of systematic reviews is the only source of biomedical publications that prohibits industry funding of the review and *BMJ* is the only other example that will not accept papers reporting on tobacco industry-funded research.[5]

Switching gears, Grundy discussed a study she and her colleagues conducted that offers insights into how to reimagine research conduct such that the public sector takes a leading role. During the early days of the pandemic, convalescent plasma from people exposed to COVID-19 emerged as a promising stopgap measure while the world waited for vaccines and other treatment options to become available. Two main approaches existed to study whether it was effective. On the public side, blood services, hospitals, and academic researchers were collecting plasma for direct transfusion, but the for-profit plasma industry was interested in developing a hyperimmune immunoglobulin isolated from plasma.

The goal of her study was to understand the social processes of clinical trial governance for this type of natural experiment with diverse players involved. Grundy considers the result a possible approach for public sector drug development and innovation in biopharmaceutical research. Her team found that almost all the trials were nearly exclusively publicly funded by government and nongovernmental actors. Industry led the hyperimmune globulin work, though it partnered with the NIH, which funded and conducted the trial with drugs provided by industry.

Grundy explained that because no manufacturer was involved in the publicly funded trials, they had no complex negotiations around acquisition, pricing, and supply. As a result, many countries placed a high priority on studies with convalescent plasma due to equity considerations. Grundy said that this illustrates that agenda setting and the involvement

[5] https://blogs.bmj.com/bmj/2018/11/12/lisa-bero-more-journals-should-have-conflict-of-interest-policies-as-strict-as-cochrane/ (accessed February 23, 2023).

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of industry sponsors is inherently about the resource distribution, who benefits, and who is at risk.

The convalescent plasma trials in different national contexts illustrated different values guiding study design and eventual outcomes, said Grundy. Sometimes, the discussion was around prioritizing clear generation of evidence. The United Kingdom, for example, conducted large, integrated health system adaptive trials; the United States, which prioritized access and establishing safety, launched a large observational trial through an Emergency Access Program. Grundy explained that she sees both sets of values as legitimate and oriented toward the public's interest, but each has implications for stewardship of resources and generating meaningful research results. "At the end, the takeaway is the need to think about clear, transparent, and accountable processes for making these values explicit and ensuring representation of the communities who are actually involved," said Grundy, who added that accountability needs to be guided explicitly by public interest.

Another feature of these publicly funded trials that was qualitatively different was their reliance on public infrastructure, such as NIH and trial networks established for other diseases. Grundy noted that the authors of a large trial in India stated that "reputed elite institutions, first-world collaborations, third-party organizations, or big funding are a big help if available, but they are not indispensable."

Grundy argued that framing the problem as needing to replace the large investment that industry has in clinical trials is insurmountable because of a lack of political will, "but I think it is also interesting to think about what research is actually needed, what is the priority, what resources are in place, and how can we leverage those most effectively." In addition to generating research results, the convalescent plasma trials also generated infrastructure and capacity within the countries that ran them. "This is consistent with where we see generally with public sector investment in research, in basic research training, and capacity building," said Grundy, who also noted the substantial openness in these high-profile studies, which again contrasts with the status quo. Networks and investigators shared trial protocols openly, and most had public-facing websites that enabled Grundy and colleagues to access study documents. Most of the studies said their data were available upon reasonable request, which was not quite the degree of openness required for an open science approach or reproducibility, but they also released their findings via preprint, press release, and Twitter to make them widely available.

Convalescent plasma became a high-profile treatment, a story involving entertainment stars, cruise ships, and black markets, said Grundy. Political decisions in India and the United States made plasma available outside of formal trials, resulting in a surge in demand and creating com-

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petition for trial participants. Each analyzed study, however, published its results in high-impact, open-access journals despite plasma not being effective in many but not all studies. Treatment guidelines incorporated this evidence rapidly, and the change in practice happened despite political pressures.

In conclusion, the story of these studies provides a different model for biomedical research. "I think this helps us reframe the purpose of health research and ultimately sponsorship," said Grundy. "We do not need to think about these as positive or negative trials; we needed to answer a question in a timely way, and important way, and we were able to develop a definitive answer." To Grundy, this is an example of public sector innovation that is mission oriented and prioritizes equity, affordability, and access. "I would argue that stewardship of resources and equity should be notions we further build into an idea of research integrity," she said. "We need to think of research, particularly health research, in the context of health systems and public health capacity and the role of public funding in relying on but also building and generating these public good."

PROTECTING THE SCIENTIFIC INTEGRITY OF THE IARC MONOGRAPHS[6]

The *International Agency for Research on Cancer* (IARC) is the specialized cancer agency of the World Health Organization and the objective of IARC is to promote international collaboration in cancer research.[7] The monographs program, explained Vincent Cogliano, are a 50-year-old series of scientific reviews identifying environmental factors that influence the risk of human cancer. The monographs are developed by the experts who conducted the original research, and they are used by national and international health agencies to support actions that prevent exposure to these compounds. In 2003, around when Cogliano joined IARC, *The Lancet* had published an editorial that said, "It only needs the perception, let alone the reality, of financial conflicts and commercial pressures to destroy the credibility of important organizations such as IARC and its parent, WHO" (Lancet, 2003).

As Cogliano recalled, he and his colleagues took this comment seriously. At the time, several approaches existed for addressing COIs, one of which was to ignore the issue, which fewer organizations are doing today. Some organizations required only disclosure, and some required disclosure but checked to make sure that not too many experts had conflicts. Some tried to balance experts with COIs with those without, and

[6] This section is based on the presentation of Vincent Cogliano, California EPA Office of Environmental Hazard Assessment.

[7] https://www.iarc.who.int/cards_page/about-iarc/ (accessed April 21, 2023).

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others tried to balance experts with COIs with an expert with an opposing interest. IARC, he said, tried to avoid COIs completely.

Cogliano identified a tension between competing ideals. "Do you want IARC evaluations of carcinogenicity developed by the most qualified experts, or you want them developed by experts whose impartiality is beyond question?" he said. "The public needs to be confident that experts with a conflicting interest have put the public interest ahead of that conflicting interest." If that is not easy to do, IARC tries to minimize the role of the conflicting interest.

Cogliano noted that this has become a more visible issue because interested parties have sponsored many of the epidemiologic and experimental studies or reanalyses of earlier studies. On the one hand, this creates a challenge because selecting experts with a real or apparent COI could erode confidence in the integrity and impartiality of the results. On the other hand, omitting prominent experts can create the perception of reduced scientific quality, a concern he heard when he spoke about IARC's approach at scientific meetings.

IARC's solution to achieving both ideals has been to create a new category of participant: the invited specialist. Cogliano explained they have critical knowledge and experience but are recused because of a COI from certain review committee activities, such as drafting any text that summarizes or interprets cancer data or developing conclusions. IARC has invited these specialists to meetings in limited numbers to contribute unique knowledge and experience and occasionally develop a chapter on production and use or compile other exposure information.

In short, said Cogliano, invited specialists are a resource that the committee can ask about details of a study that may not appear in a published paper. In this way, IARC meetings include the best-qualified experts, but the monographs and conclusions are developed by experts without COIs. The invited specialist role also protects the integrity of scientists affiliated with interested parties, since they are present as a resource, not to influence the outcome, and therefore have no responsibility for an evaluation that might not end how their company wants.

The process for selecting experts to participate on review committees starts with a literature search and public nominations to identify potential experts. All of them submit a declaration of interests; if they have no COIs, they may be invited to join. If a COI exists, IARC looks for a comparable expert; if necessary, the expert with a COI may be an invited specialist, explained Cogliano. All declarations are updated and reviewed again at the committee meeting.

IARC uses several criteria for what constitutes a COI: whether the expert was employed by an interested party over the previous 4 years; has consulted or given expert testimony on matters before a court or

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government agency; and has a financial interest, such as owning stock, or relevant intellectual property, such as patent rights. IARC also looks at support for an expert's own research and support for others in their research unit or organization. As an example of the latter, Cogliano said that the chair of a department who does not work on a particular project but whose department has a grant from a sponsor would have a COI.

In addition to the declaration of interest, IARC will often call a potential expert and ask questions that could reveal a pattern of activities that might suggest an ongoing relationship, such as participating in a few workshops with the same group of people that includes those with COIs. IARC also examines the acknowledgment sections of recent papers to identify possible supporters and searches the Internet for links to the expert. For example, one potential expert for a monograph on estrogen and progestogen contraceptives and hormone therapy who did not declare a COI was featured in a set of what were essentially marketing meetings advertising the use and safety of a particular contraceptive device. Finally, said Cogliano, IARC staff reviews what constitutes a COI at the committee meeting to ensure that committee members truly understand.

IARC has seen various attempts to game the process, said Cogliano. Occasionally, reanalyses appear in journals a week before a committee meeting in which the results are less positive than they were in the original papers. Interested parties also sponsored an ad hoc conference a few weeks before a monograph meeting to which four or five of the selected experts were invited to attend and spend several days with the special interest. "Somebody once showed me a letter about honoraria that they were being paid that said if you would rather this not show up so you do not have to declare it, we can adjust your travel reimbursement to cover this," Cogliano recounted. Interested parties have also sent staff to Lyon, France to monitor a meeting and tried to communicate with a specialist there.

IARC also has a process for independent reporting of COIs by a third party that he believes holds great promise for ensuring that organizations adopt a strong policy and do not backslide. At a monograph meeting, IARC asks experts to update their declarations and to complete *The Lancet Oncology's* COI form; the editor independently reviews the COI statements and reports any COIs alongside a published summary of the meeting (Cogliano et al., 2005).

Before a meeting, IARC posts a list of committee members on its website along with the following message: "IARC requests that you do not contact or lobby meeting participants, send them written materials, or offer favors that could appear to be linked to their participation... IARC will ask participants to report all such contacts and will publicly reveal any attempt to influence the meeting" (Cogliano et al., 2005). IARC also reminds committee members in its invitation to participate letters and

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during the meeting to safeguard the integrity of everyone's work by resisting and reporting all attempts at interference. Finally, it includes a statement in a preamble to the monographs: "It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time." The hope is these actions serve as a deterrent to lobbying participants either before or during a meeting, said Cogliano.

One reaction in response to these procedures came from *The Lancet Oncology* in 2005, 2 years after it first voiced its concerns about any perception of a COI. After reviewing the steps IARC had taken, the journal's editor wrote that they were "an important step toward restoring trust in the way that results of studies done by publicly funded agencies are both prepared and reported. The issues encountered by IARC are certainly not unique, and we hope that this joint initiative will serve as a model for other health agencies" (Collingridge, 2005). EPA has even adapted the IARC process for contractor-managed peer reviews.[8]

Cogliano said that good research studies are not sufficient. "We also need good review committees who are composed of knowledgeable experts who are free from conflicting interests and who can work free from interference," he said. "Not only must we reach an appropriate conclusion, but we must also do so in a transparent manner that promotes public confidence."

MINIMIZING BIAS IN AHRQ EVIDENCE-BASED PRACTICE CENTER PROGRAM SYSTEMATIC REVIEWS[9]

Umscheid explained that the Agency for Healthcare Research and Quality (AHRQ) is one of 11 agencies in the Department of HHS and that it its mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable and to work with partners to ensure that the evidence is understood and used. AHRQ established the Evidence-Based Practice Center (EPC) Program in 1997. The program has provided systematic reviews of published scientific evidence on a range of health topics for a variety of requesters and invests heavily in methods development for evidence reviews. Reviews and methods work are contracted to nine academic research organizations (Table 5-1). The EPCs, said Umscheid, play a big part in ensuring rigor and minimizing bias in AHRQ's reviews, as do the AHRQ EPC Division's staff members, who have expertise and experience in the clinical topics reviewed by EPCs

[8] Details of EPA's process are available at https://www.epa.gov/sites/default/files/2015-01/documents/epa-process-for-contractor_0.pdf (accessed February 2, 2023).

[9] This section is based on the presentation of Craig Umschied, Agency for Healthcare Research and Quality.

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TABLE 5-1 Current AHRQ-Funded Evidence-Based Practice Centers

- Brown University
- ECRI Institute—Penn Medicine
- Johns Hopkins University
- RTI International—University of North Carolina, Chapel Hill
- Mayo Clinic
- University of Minnesota
- Oregon Health and Science University
- Kaiser Permanente Research Affiliates
- University of Southern California—RAND Corporation

SOURCE: Umscheid Slide 5, Effective Health Care Program, 2021.

and in systematic review methods. He noted that the impact of the EPC program depends on the trust users have in its products and the partners who work with the EPCs, which include guideline developers both within and outside of the federal government, such as professional societies.

The EPC Program has worked with over 100 unique partners and completed over 800 evidence reviews in its 25-year history. These reviews have informed approximately 200 U.S. Preventive Services Task Force guidelines, 200 clinical practice guidelines issued by federal and professional society partners, 35 Medicare National Coverage Determinations, and 40 NIH research prioritization meetings, said Umscheid.

An AHRQ EPC systematic review is a summary of overall evidence to address a set of key questions identified, explained Umscheid. It is protocol driven and starts with a comprehensive search of existing peer-reviewed studies. EPCs appraises each study critically and summarizes findings for each key question addressed across all important outcomes, including benefits and harms. EPC methods are based on the National Academy of Medicine's Standards for Systematic Reviews,[10] which AHRQ helped fund.

Umscheid categorized the systematic review process into five main steps: preparing the topic, searching for and selecting studies for inclusion, extracting data from the studies, analyzing and synthesizing the studies, and reporting the findings. EPC does significant work preparing and refining the topics, which supports transparency, improves rigor, and minimizes bias. Most reports EPC prepares are triggered through a request from a federal agency to inform a federal policy or decision or nomination

[10] Available at https://nap.nationalacademies.org/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews (accessed February 2, 2023).

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by the public. He noted that EPC receives so many of the latter that it has a selection process that is as transparent as possible to minimize bias.

The topics must be appropriate for review in that they are related to U.S. health care interventions that address significant disease burden or vulnerable populations and have high interest or cost, said Umscheid. An additional requirement is no recent systematic review on the topic but existing studies that EPC can synthesize. An end user partner must be identified who will help shape the review and disseminate and implement it to produce change.

EPC puts a great deal of effort into scoping the key questions, with a focus on increasing rigor and transparency and minimizing bias. This involves fleshing out the target population, specific interventions, and comparators and the outcomes to include. EPC relies on experts to inform the scope of the review; the experts must disclose financial and other relevant COIs. "Because of their unique content expertise, those with potential conflicts may still be retained to help us scope the protocol," said Umscheid. "We aim to balance, manage, and mitigate potential conflicts of interest across the expert panel that is going to inform the protocol for review."

As an example, Umscheid discussed a recent report developed in partnership with the American Epilepsy Society and the Patient-Centered Outcomes Research Institute (PCORI) that evaluated interventions for managing infantile epilepsies. This topic met all the selection criteria, and EPC worked with pediatric neurologists and neurosurgeons, epilepsy nurse practitioners, dietitians, Ph.D.'s involved in epilepsy research, and the executive director of a family advocacy foundation to scope the review. The review focused on children aged 1 month to 3 years old; assessed pharmacologic, dietary, surgical, and other interventions; and looked at both intermediate and patient-centered health outcomes and adverse effects of the interventions.

After creating the review protocol, EPC conducts a comprehensive search of the peer-reviewed literature. For the infantile epilepsy review, this search identified 11,000 records, 41 of which were included. Two individuals then screen the studies independently against agreed-upon eligibility criteria, said Umscheid, and two others extract agreed-upon data from those studies.

EPC uses standardized risk-of-bias assessment tools for each of the selected studies. Umscheid explained that EPC used the Cochrane Risk of Bias 2 tool for randomized controlled trials and the Risk of Bias in Non-Randomized Studies of Interventions tool. These tools assess the similarity between test and control groups at baseline, adherence of groups to assigned interventions, completeness of outcome assessments in each study group, and blinding of those prescribing and receiving interventions and those evaluating outcomes. These risk-of-bias assessments (see Figure 5-3) can help identify and mitigate bias resulting from COIs by

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Trial and Outcome	Generation of Randomization	Allocation Concealment	Baseline Imbalance	Patient Blinded	Staff Blinded	Differential Ancillary Treatments	Adherence	Analytic approach to address deviations from	Data On At Least 80% of those Enrolled	Differential Dropout <=15%	Standard Way To Measure The Outcome	Blinded Outcome Assessor	Bias In Selection Of Reported Results	Overall Risk of Bias
Liu et al. (2020)[1584] Seizure freedom	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	Low	High
Liu et al. (2020)[1584] Quality of life	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	Low	High
Novotny et al. (2010)[1584,1585] Adverse events	Low	Low	Low	Low	Low	SC	Low	Low	Low	Low	Low	Low	Low	Low
Manitpisitkul et al. (2013)[1586] Adverse events	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	High	Low	Moderate
Liu et al. (2020)[1584] Adverse events	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	SC	High
Pina-Garza et al. (2008)[1585,1586] Adverse events	SC	SC	SC	Low	Low	Low	SC	Low	Low	Low	Low	Low	Low	Moderate

FIGURE 5-3 Risk-of-bias table for randomized controlled trials on pharmacologic interventions for infantile epilepsy
NOTE: SC = some concerns.
SOURCE: Presented by Craig Umscheid on December (Effective Health Care Program, 2022).

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determining whether studies are selecting specific designs and hypotheses to favor the treatment over the control, such as by picking inferior comparison drugs and doses or selectively reporting outcomes, including certain outcomes from multiple available end points or using composite end points without presenting data on individual end points.

The risk assessments allow the reviewers to explore different results between higher and lower risk-of-bias studies. If the outcomes are essentially the same, that provides more certainty regarding the findings, said Umscheid. Risk of bias can also enable grading of the overall strength of the evidence for the interventions. Doing so for interventions across all studies by outcomes considers factors such as study design informing the outcome, the consistency of studies examining the outcome, the precision of the results, and the magnitude of the effect. Figure 5-4 shows the strength-of-evidence table for the outcome of "freedom from seizure."

Umscheid said that once the draft report is complete, EPC releases it and posts it on its public website[11] to provide the opportunity for public comment; it also undergoes peer review. When the final report is released, EPC reports a disposition of the comments received during the public comment process. "Stakeholder engagement and transparency throughout this process helps us increase the rigor and minimize potential bias of our reports," said Umscheid. Many reports are also accompanied by interactive visual dashboards on the EPC website.

PANEL DISCUSSION: PROTECTING THE INDEPENDENCE OF RESEARCH

Comments on the Presentations

Woodruff listed themes from the presentations about structural solutions to the problem of sponsors influencing research, starting with the need for public funding. To ensure research is not being influenced by a financial interest, both the research enterprise and the people conducting the research need to be publically funded, Woodruff said. She noted that the pace of public funding, such as grants from NIH, have not kept up with the cost of research, creating pressure on academics to seek other sources of funding.

Woodruff said that as NIH underwrites work that looks at the rigor of research, it should also fund areas to understand how its funding influences financial COIs. She noted the importance of access to the truth, which requires public access to industry documents. Many of the presentations illustrating how corporate interests influenced the scientific process were only possible because of access to internal industry docu-

[11] https://effectivehealthcare.ahrq.gov/ (accessed February 2, 2023).

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Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Levetiracetam (LEV)	Seizure freedom	One RCT[33] N=100 reported seizure freedom rates of 32% (16/50) with LEV+valproate vs 22% (11/50) with valproate alone (odds ratio 1.7, 95% CI 0.7 to 4.1) One pre/post study[34] reported 66% seizure freedom (61/92)	High	Direct	Consistent	Precise	None suspected	None	Low	Adding levetiracetam may cause seizure freedom in some infants
Levetiracetam (LEV)	Quality of life	One RCT[33] N=100 reported QOL scores of scores 84 with LEV+valproate vs 80 valproate alone (12 week follow-up) (statistically significant)	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Topiramate	Seizure freedom	One non-randomized comparative study[35] reported 59% seizure freedom (24/41) One pre/post study[37] reported 19% seizure freedom (11/58) One pre/post study[38] reported 8% seizure freedom (3/37)	High	Direct	Inconsistent	Imprecise	None suspected	None	Insufficient	NA
Topiramate vs carbamazepine	Seizure freedom	One non-randomized comparative study N=146;[36] topiramate 59% (24/41) vs carbamazepine 55% (58/105)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

FIGURE 5-4 Strength-of-evidence table for trials on pharmacologic interventions for infantile epilepsy.
SOURCE: Presented by Craig Umscheid on December (Effective Health Care Program, 2022).

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ments archived at public institutions, such as UCSF. Woodruff called for supporting these archives and working to make litigation-disclosed documents public. The latter, she said, can help create accountability for how interests have influenced and evaluated science. She also suggested expanding the public registries for competing financial interests to other areas beyond pharmaceuticals and U.S. clinicians.

Woodruff noted that just because meta-research finds that a COI leads to a bias in the results does not mean excluding the findings from further analysis, but it does mean accounting for potential bias in evaluating the evidence. She also called the discussions about declarations of COI eye opening, particularly the research showing that declarations are insufficient. She appreciated the recommendations to investigate this issue and norming values about why it is important.

Her final comment was about representation and who is at the table when having these conversations. In the environmental health field, for example, the communities experiencing harm should be represented in these meetings, as should the environmental justice community.

Lexchin discussed areas that he believes should be the focus of reform. The first involves leadership; he noted a failure of medical leadership around the issues the workshop has discussed. For example, an investigation of financial COIs for 328 leaders of 10 leading U.S. professional disease-focused organizations found that two-thirds had financial COIs and received $135 million from industry sources, with a median of about $32,000 per person (Moynihan et al., 2020). "When you have conflicts at the top, those organizations may not be willing to confront problems associated with those conflicts and bias in the outcome of research," said Lexchin. Similarly, a study Lexchin participated in found that societies involved in sponsoring clinical practice guidelines in Canada were not disclosing their industry funding in the guidelines, though they did so on their websites (Elder et al., 2020).

Medical journals also need reform when it comes to identifying COIs, said Lexchin. He noted that the U.S. Centers for Medicare and Medicaid Services maintains the Open Payments database, which allows anyone to search payments made by drug and medical device companies to physicians, physician assistants, advanced practice nurses, and teaching hospitals.[12] He wondered if medical journals use the database to identify COIs among the authors of the studies they are considering publishing. "There is good literature that shows there is under-reporting of COIs by authors, so we need to encourage medical journals to look and use that database to look for where those undisclosed conflicts are," he said.

[12] https://openpaymentsdata.cms.gov/ (accessed February 2, 2023).

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In addition, said Lexchin, most major medical journals do not disclose the details of their funding sources, such as how much money they get from advertising, the sales of reprints, and other sources that may include industry, and he called for them to disassociate themselves from industry funding. He calculated the advertising revenues that the *Canadian Journal of Emergency Medicine* received and determined that it could eliminate all pharmaceutical company advertising if it charged $50 more per person for membership in the Canadian Association of Emergency Physicians (Lexchin, 2009). The journal dismissed this idea, saying it had no trouble with drug company promotion.

One approach for dealing with this, which Sah mentioned, is to go beyond disclosing COIs and eliminate them by introducing policies at the level of medical schools and hospitals to ensure a separation between students and trainees and industry. Lexchin said that a few studies have looked at the long-term consequences of restricting contact and found that clinicians trained at institutions with such a policy were less likely to interact with industry, prescribe new and relatively untested drugs, and believe the information they received from industry (McCormick et al., 2001, 2002). Given this, he encourages medical schools and hospitals to introduce strict policies that separate their trainees and students from industry. However, he noted that when McMaster University's general internal medicine residency program did so in the early 1990s, with agreement from the residents, the brand-name industry association threatened to withdraw research funding.

Lexchin raised the issue of industry support for clinical trials of drugs and how that might affect pharmaceutical product approvals. He acknowledged that public funding of drug trials would address this problem, but that would require a major increase in public funding. A parallel approach would be to change how companies think about their research; he proposed introducing a medical need clause into regulatory requirements, which Norway did at one time (Hobæk, 2019). That clause would reject products that were no more efficacious, safe, or convenient than currently available products. In his view, if the major regulatory authorities started to do that, industry might change how it does research.

He also called for strengthening the standards of regulatory agencies, increasing public funding for them, and eliminating industry user fees. That might make a difference in how regulatory agencies approach the research they review (Gaffney et al.). "If they are being more strict with the research, then companies will modify the way they do their research," said Lexchin. In addition, clinicians should stop relying on publications and turn to the clinical study reports, which provide much more information (Wieseler et al., 2012, 2013).

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Discussion

Responding to Lexchin's comments on industry user fees, Redberg explained that FDA negotiates its fee agreements with industry behind closed doors. "There is no public there, and there is no negotiation of the rest of the FDA agenda with the public with the recognition that it is a taxpayer-supported agency," said Redberg. "I think that is just a huge problem, and it makes it seem as if the FDA works with industry, not as a protector of public health."

Sah said she agreed wholeheartedly with the suggestions that Woodruff and Lexchin made, and that public funding is a key aspect. She commented on industry threats to withdraw funding if new policies restrict access to research or clinicians and said this will be difficult to tackle without a big shift in how research is conducted, which needs a coordinated approach. Woodruff agreed that more public funding is needed and added that an industry fee should be paid to an independent agency, such as FDA, though not through the current process, as described by Redberg. Rather, the fees could go through a public process. Lexchin noted that Italy funds drug research via a 5 percent tax on the amount that companies spend on promotion (AIFA Research & Development Working Group, 2010). Given estimates that pharmaceutical companies spent nearly $30 billion in 2016 on promotion (Schwartz and Woloshin, 2019), 5 percent would be $1.5 billion.

Grundy supported that idea and noted models for shoring up public institutions, along with a need for more public representation in the operations of public institutions that work in the public interest. Today, it occurs largely through patient representatives who are often sponsored by industry or other commercial interests. "I think we need to rethink about the ways that not just patients, but publics are involved in setting research agendas and asking the questions that are important in the priorities and in the research itself," said Grundy.

Sah commented on the decrease in public trust in science and experts in science, which was apparent during the COVID-19 pandemic, and the connection to COIs and representation, particularly increasing representation in clinical trials. "I think both the public trust and the representation aspect are key things to consider moving forward," said Sah.

Bero raised the idea of less is more in terms of research and if that would help with evidence synthesis. "If we have research focused on the important public health–relevant questions, is it really better for us than just having a lot of funding for research that we do not really need?" Bero asked.

Redberg thought that was a fabulous idea. She also commented that she hears from industry that if it does not drive the research agenda, it will stymie innovation and developing new drugs. "'Innovation' is used

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incredibly loosely, and anything new is called 'innovation,'" she said. What industry is really talking about is pushing things to market that are not well studied but supported by experts who received millions in funding to say it is good. In her view, it is not a given that we need more drugs to treat the same condition.

Umscheid pointed out that much of the work EPC does involves building relationships with funding organizations to communicate identified evidence gaps back to those institute leaders to help them prioritize their research agenda. He added that all of EPC's systematic reviews include appendixes with information on studies' funding sources. However, EPC does not automatically rate industry-sponsored studies as having a high risk of bias because unrelated causes of such risk may exist. Instead, EPC uses the validated tools he described to look at differences between groups and how interventions, comparators, and outcomes are defined.

Bero mentioned Dunn's work on automated tools to identify risk of bias and how funding source and COI would be characteristics fed into those tools to assess risk for an individual study. She added that it is important to distinguish between the risk in individual studies and the types of bias seen across a body of studies, such as publication or funding bias.

Gunsalus asked Sah to address an audience question about whether the pooled funding model leads to COIs at the institutional level and makes universities, rather than the individual investigators, beholden to their corporate sponsors. Sah identified institutional COIs where they are chasing gifts and other types of fundings from corporate sponsors. It is important to question how that money will be used, about any blinding and separation, and if pooled funding will affect how whoever accepts the money conducts their day-to-day activities. Other questions include whether the sponsor influences any aspects of how the university is run, its relationship with the sponsor, and how much feedback the sponsor gives it. "Those are the questions that we need to ask with regards to sort of institutional level COIs, because there is the risk there will be an attempt to please certain sponsors so you can get more income in the future," said Sah.

Grundy mentioned the need to think about the social context around the commercialization of academic research. She noted the qualitative social science studies reporting that investigators get the sense they are being actively encouraged to partner with industry by one policy but then feel slapped on the wrist for having a COI. "This is something well within academic and university policies that could be addressed," she said. Asked for final comments, many of the panelists noted the complexity of this issue and the need for grassroots efforts to address some of the challenges discussed.

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Appendix A

Workshop Agenda

WEDNESDAY, DECEMBER 14, 2022

SESSION 1—DO SPONSORING ORGANIZATIONS INFLUENCE RESEARCH?
Session Moderator: Lonnie King, the Ohio State University

11:00 **Welcome**
Lonnie J. King, *The Ohio State University*

11:15 **Overview of the Evidence on Sponsor Influence**
Lisa Bero, *University of Colorado*

SESSION 2—PROTECTION OF RESEARCH INTEGRITY
Session Moderator: Aaron Kesselheim, Harvard

12:15 **Research Integrity in Extramural Research at the National Institutes of Health**
Patricia Valdez, *National Institutes of Health*

12:35 **Gaining Sponsor Support, While Maintaining Scientific Independence**
Daniel Greenbaum, *Health Effects Institute*

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12:55 **Application of Corporate Ethical Policies and Governance Processes, with a Focus on Bioethics**
Clive Green, *Astrazeneca U.K.*

1:15 **Panel Discussion: Where Are the Points of Influence on Scientific Research**
Session Speakers Above; Nicholas Chartres, *University of California, San Francisco*; Gary Ruskin, *U.S. Right To Know*

THURSDAY, DECEMBER 15, 2022

Session 3—Examples of Sponsor Influence of Health Research

Session Moderator: Ross McKinney, Association of American Medical Colleges

11:05 **Protecting Public Health in the Face of Corporate Disinformation**
David Michaels, *George Washington University*

11:25 **The Intended and Unintended Consequences of Health Technology and Observational Real-World Evidence**
Adrian Hernandez, *Duke*

11:45 **Industry Funding Bias in Nutrition Science on Ultraprocessed Foods: A Cautionary Tale**
Laura Schmidt, *University of California, San Francisco*

12:05 **It's What You Don't See That Counts: A Peek Behind the Smokescreen**
Martin Mckee, *London School of Hygiene and Tropical Medicine*

12:25 **Can Data and AI Make it Easier to Manage the Impacts of Conflicts of Interest?**
Adam Dunn, *University of Sydney*

12:45 **Sponsor Influence in Diabetes Research: An Industry Case Study**
Dean Schillinger, *University of California, San Francisco*

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1:05 **Panel Discussion**
Session Speakers Above; Cary Gross, *Yale University*

2:00 **Adjourn**

FRIDAY, DECEMBER 16, 2022

Session 4—Models, Processes, and Principles Used to Protect the Independence and Quality of Research

Session Moderator: C. K. Gunsalus, National Center for Professional Research Ethics

11:00 **Welcome**
C. K. Gunsalus

11:05 **A Deep Dive into Professionalism: Policy Solutions to Conflicts of Interest**
Sunita Sah, *Cornell*

11:30 **Role of the Sponsor (Funder) in Research Studies**
Rita Redberg, *University of California, San Francisco*

11:55 **Alternatives to Industry: Seeking Independence in Biopharmaceutical Research**
Quinn Grundy, *University of Toronto*

12:20 **Protecting the Scientific Integrity of the IARC Monographs**
Vincent Cogliano, *CalEPA Office of Environmental Health Hazard Assessment*

12:45 **Addressing Conflicted Research in Evidence Synthesis**
Craig Umscheid, *Agency for Healthcare Research and Quality*

1:10 **Panel Discussion: How to Protect Independence of Research**
Session Speakers Above, Tracey Woodruff, *University of California, San Francisco*; Joel Lexchin, *York University Toronto Canada*

2:00 **Adjourn**

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Appendix B

Biographical Sketches of the Moderators and Speakers

Lisa Bero, Ph.D., is chief scientist at the Center for Bioethics and Humanities and professor of medicine and public health at the CU Anschutz Medical Center and senior editor for research integrity for the Cochrane Collaboration. She is a leader in evidence synthesis, meta-research and studying commercial determinants of health, focusing on tobacco control, pharmaceutical policy, and public health. Dr. Bero has developed and validated qualitative and quantitative methods for assessing bias in research design, conduct, and dissemination and pioneered using internal industry documents and transparency databases to understand corporate tactics and motives for influencing research evidence. She has authored academic articles with a focus on research integrity topics, including measuring problems with it (methods issues, COIs, "spin"), testing methods to improve it (training, policy development), and assessing how research is used or cited (in policy, media, or scientific literature). She has served on international committees for the National Academies, IARC, and WHO.

Nicholas Chartres, Ph.D., is the director of science and policy for PRHE, which monitors and analyzes federal, state, and local chemical policy, including EPA's implementation of the Toxic Substances Control Act, which evaluates and regulates industrial chemicals used in U.S. commerce. He has extensive experience in systematic review methods and leads PRHE's work in disseminating and implementing them to improve evidence evaluation in the environmental health sciences and ensure the best available science is used for policy decision making. As the lead

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author of the first in-depth study on how industry sponsorship influences nutrition research, he is an expert in identifying and analyzing industry influence and developing methods to reduce industry bias in the research process. Dr. Chartres is also part of the WHO/International Labor Organization Joint Estimates Working Group examining global work-related burden of disease and injury. He earned a Ph.D. from the University of Sydney.

Vincent Cogliano, Ph.D., has served since December 2019 as California EPA's Office of Environmental Health Hazard Assessment deputy director for scientific programs; he manages its scientific programs and essentially functions as its chief scientist. He brings more than 35 years of experience at federal and international health agencies in assessing environmental health risks. Dr. Cogliano worked for more than 25 years at the U.S. EPA, where he directed its Integrated Risk Information System program, which identifies adverse health effects of chemicals in the environment and conducts analyses to support the protection of human health. He also served as deputy to the agency's scientific integrity official. His professional interests include qualitative and quantitative health risk assessment and the application to the protection of public health, especially in children and susceptible populations. He received his Ph.D. from Cornell University.

Adam Dunn, Ph.D., is an associate professor in the Faculty of Medicine and Health and leads Biomedical Informatics and Digital Health at the University of Sydney. He works broadly across biomedical informatics using multidisciplinary tools and methods but most often in applications of machine learning and natural language processing. His key interests are in public health informatics, especially research about misinformation and health behaviors, and clinical research informatics, especially about reducing bias and increasing timeliness of evidence synthesis from clinical trials. He has led or co-led research projects funded by the NHMRC, AHRQ, NLM/NIH, and WHO; is the Convener of the Digital Health and Informatics Network at the University of Sydney; is affiliate faculty with the Computational Health Informatics Program at Boston Children's Hospital; and has held editorial roles with a range of medical journals and computer science conferences. He earned a Ph.D. from the University of Western Australia.

Clive Green, Ph.D., is executive director of Biopharmaceuticals Research and Development at AstraZeneca, where he leads research chemical synthesis using automated technologies and the global processing and distribution of research molecules. Dr. Green is also chair of AstraZeneca's

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Governance Team for the Nagoya Protocol, which ensures the benefits from the use of nonhuman genetic resources (plant, animal, microbial, or other origins containing functional units of heredity) are shared fairly and equitably and Bioethics Advisory Group, which provides advice, support, and guidance to the company's scientists, project teams and leaders on bioethical issues. He received his Ph.D. from the University of Nottingham, U.K.

Daniel Greenbaum is president of HEI, where he leads its efforts to provide public and private decision makers—in the United States, Asia, Europe, and Africa—with high-quality, impartial, relevant, and credible science about the health effects of air pollution to inform air quality decisions in the developed and developing world. He works with HEI's sponsors in government and industry, its scientific committees and staff, and other environmental stakeholders to develop and implement its Strategic Plan for Understanding the Health Effects of Air Pollution, which sets HEI's course every 5 years. He was commissioner of the Massachusetts Department of Environmental Protection, responsible for the Commonwealth's response to the Clean Air Act and its award-winning efforts on pollution prevention, water pollution, and solid and hazardous waste. He received his M.S. in city planning from the Massachusetts Institute of Technology.

Cary Gross, M.D., is a professor of medicine and public health and director of the National Clinician Scholars Program at Yale. His research addresses research integrity, comparative effectiveness, quality, and health equity, with a focus on cancer prevention and treatment. He aims to use real-world research to generate knowledge that will inform change in clinical care and health policy. He is a founding Director of Yale's Cancer Outcomes Public Policy and Effectiveness Research Center. In the realm of research integrity, Dr. Gross has investigated the relation between financial COIs and study outcomes, ethical issues in disclosing financial ties to patients, and clinical trial data sharing. He earned his M.D. from New York University.

Quinn Grundy, Ph.D., R.N., is assistant professor in the Lawrence S. Bloomberg Faculty of Nursing at the University of Toronto. Her research explores the interactions between medically related industry and public health systems and the impacts on the delivery of health services, health evidence, and consumer health information. Dr. Grundy is the author of *Infiltrating Healthcare: How Marketing Works Underground to Influence Nurses* (Johns Hopkins University Press, 2018). She earned a Ph.D. from USCF.

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C. K. Gunsalus, J.D., is the Director of the National Center for Professional and Research Ethics (NCPRE), professor emerita of business, and research professor at the Coordinated Sciences Laboratory. She was the PI for the centerpiece project of NCPRE, Ethics CORE, a national online ethics resource center. She has been on the faculty of the colleges of Business, Law, and Medicine at the University of Illinois at Urbana-Champaign and special counsel in the Office of University Counsel. In the College of Business, she taught Leadership and Ethics in the MBA program and was the director of the required Professional Responsibility course for all undergraduates. In law, she taught Negotiation and Client Counseling; she was a member of the faculty of the Medical Humanities and Social Science program in the College of Medicine, where she taught communication, conflict resolution, and ethics. Her experience at the university included technology transfer, management of COIs, human research participant protection, and long-term service as the campus research standards officer with responsibility for responding to allegations of professional misconduct by faculty and students. She earned a J.D. from the University of Illinois.

Adrian F. Hernandez, M.D., is a cardiologist and vice dean for clinical research at the Duke University School of Medicine. He is the coordinating center PI for the PCORI National Patient- Centered Clinical Research Network, NIH's Health System Collaboratory, and other pragmatic clinical trials to generate real-world evidence. He is also the coordinating center PI for the Baseline Health System Consortium, which aims to change how clinical research is performed to integrate people in and outside of the health system, accelerate research, and improve efficiency. Dr. Hernandez's research focus is to improve population health, focusing on understanding health outcomes and closing the gap between clinical efficacy and effectiveness. He is an expert in trial design, use of electronic health data, health services, and regulatory science and significantly contributed in the fields of heart failure, outcomes research, population health, and clinical research methodology. He is an elected member of the American Society of Clinical Investigation and Association of American Physicians. He earned his M.D. from the University of Texas-Southwestern in Dallas.

Aaron Kesselheim, M.D., J.D., M.P.H., is a professor of medicine at Harvard Medical School. He serves as a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital and a primary care physician at its Phyllis Jen Center for Primary Care. His research focuses on the effects of intellectual property laws and regulatory policies on pharmaceutical development, the drug approval process, and the costs, avail-

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ability, and use of prescription drugs both domestically and in resource-poor settings. Within the division, Dr. Kesselheim founded and leads the Program on Regulation, Therapeutics, and Law, an interdisciplinary research center focusing on intersections among prescription drugs and medical devices, patient health outcomes, and regulatory practices and the law. He received his medical and legal training at the University of Pennsylvania and M.P.H. at the Harvard School of Public Health and is a member of the New York State Bar.

Lonnie King, D.V.M., has more than 30 years of expertise in advancing the health and welfare of animals and humans. He is an innovator in veterinary education, biomedical research, and animal disease discovery. Dr. King is an expert in the "One Health" initiative and frequently serves as a keynote and guest panelist to diverse audiences worldwide regarding the convergence of human and animal health. He has also been cochair on the joint Task Force on Antibiotic Resistance in Production Agriculture to respond to the recommendations in the President's Council of Advisors on Science and Technology report on Antimicrobial Resistance. He is a member of the National Academy of Medicine. Dr. King earned a D.V.M. from Ohio State University.

Joel Lexchin, M.D., is a professor emeritus in the School of Health Policy and Management at York University in Toronto, Canada, where he taught health policy until 2016. In addition, he worked in the emergency department at the University Health Network (Toronto) for over 33 years. He is the author or coauthor of papers on a wide range of topics, including drug regulation, pharmacosurveillance, drug promotion, research and development, access to medications in developing countries, and physician prescribing behavior. He is a fellow of the Canadian Academy of Health Sciences and among the top 2 percent of the world's most highly cited researchers. He received his M.D. from the University of Toronto.

Martin McKee, M.D., is professor of European public health at the London School of Hygiene and Tropical Medicine, where he founded the European Centre on Health of Societies in Transition, a WHO Collaborating Centre. He is also research director of the European Observatory on Health Systems and Policies and president of the European Public Health Association. He was elected to the U.K. Academy of Medical Sciences, Romanian Academy of Medical Sciences, and National Academy of Medicine. Dr. McKee was awarded honorary doctorates from Hungary, The Netherlands, and Sweden, visiting professorships at universities in Europe and Asia, the 2003 Andrija Stampar medal for contributions to European public health, the 2014 Alwyn Smith Prize for outstanding con-

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tributions to population health, and the 2015 Donabedian International Award for contributions to quality of care. In 2005, he was made a Commander of the Order of the British Empire. He received a medical degree from Queens University of Belfast, U.K.

Ross McKinney, M.D., is the chief scientific officer at AAMC. He leads programs that support all aspects of medical research and training and represents AAMC nationally on issues related to research and science policy, administration, workforce development, and education and training. Dr. McKinney joined AAMC in 2016 after more than 30 years as a member of the Duke University faculty, where he was director of the Division of Pediatric Infectious Diseases, Vice Dean for research at the School of Medicine, and director of the Trent Center for Bioethics, Humanities, and History of Medicine. He earned an M.D. from Duke.

David Michaels, Ph.D., M.P.H., is an epidemiologist and professor at the Milken Institute School of Public Health at George Washington University. He was U.S. Assistant Secretary of Labor for OSHA from 2009 to January 2017, the longest-serving administrator in its history. During the Clinton Administration, Dr. Michaels was U.S. Assistant Secretary of Energy for Environment, Safety, and Health, charged with protecting the workers, community, and environment around the nation's nuclear weapons facilities. Much of his research focuses on protecting the integrity of the science underpinning public health, safety, and environmental protections. He is the author of *The Triumph of Doubt: Dark Money and the Science of Deception* (Oxford University Press, 2020) and *Doubt is Their Product: How Industry's Assault on Science Threatens Your Health* (Oxford University Press, 2008). He earned a Ph.D. from Columbia University.

Rita F. Redberg, M.D., is a cardiologist and professor of medicine at the USCF, and Core Faculty at the Philip R. Lee Institute for Health Policy Studies. She is the chief editor of *JAMA Internal Medicine* since 2009 and has spearheaded its new focus on health care reform and "less is more." Her research interests are in health policy and technology assessment and how to promote high-value care, focusing on high-risk medical devices and the need to include women in clinical trials for them. Dr. Redberg served on the Medicare Payment Advisory Commission to Congress. She also served and chaired the Medicare Evidence, Development, and Coverage Advisory Committee. She has given Congressional testimony multiple times in hearings on the issue of balancing safety and innovation in medical device approvals. She worked in the office of Senator Hatch and with the Senate Judiciary Committee on FDA-related matters during her tenure as a Robert Wood Johnson Health Policy Fellow (2003–2006). Dr.

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Redberg is a member of the National Academy of Medicine. She earned a medical degree from the University of Pennsylvania.

Gary Ruskin is the executive director and cofounder of U.S. Right to Know, a nonprofit public interest investigative research group. He has coauthored 15 studies on corporate influence on research and health organizations, corporate science denial, disinformation, and product defense. He directed the Congressional Accountability Project, which opposed corruption in the U.S. Congress. He earned a master's degree in public policy from Harvard.

Sunita Sah, M.D., is a professor and organizational psychologist at Cornell University, director of Cornell's Academic Leadership Institute, and a fellow at the University of Cambridge. Dr. Sah's research expertise is in COIs, disclosure, influence, professionalism, consent, compliance, and trust. She teaches leadership, negotiations, and critical thinking and is on the scientific advisory board of the Behavioral Economics in Health Network, on the advisory board of the International Behavioral Public Policy Association, a fellow of the Society of Personality and Social Psychology, and on the editorial board of the journal *Behavioral Public Policy*. Dr. Sah served as a commissioner on the National Commission of Forensic Science and on the Human Factors Committee for the National Institute of Science and Technology Forensic Science Standards Board. She holds a Ph.D. from Carnegie Mellon University and an M.B. Ch.B. (U.K. equivalent to the U.S. M.D.) from the University of Edinburgh.

Dean Schillinger, M.D., is a general internist, primary care physician, and UCSF professor of medicine. He is an international research expert in chronic disease–related public health, health communication, dissemination science and health policy. He recently completed a term as chief of the Division of General Internal Medicine at San Francisco General Hospital and was chief of the Diabetes Prevention and Control Program for California. He co-directs a National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)-funded Center for Translational Research (Diabetes Research for Equity Through Advanced Multilevel Science). Of Chilean descent, he has extensive experience working with Latinx, Black, and Asian and Pacific Islander populations. He co-created a youth-led diabetes prevention social media campaign, The Bigger Picture (www.thebiggerpicture.org), which merges arts with public health to catalyze social action; it was recognized by the National Academy of Medicine and received WHO's Non- Communicable Disease Lab Award. Dr. Schillinger recently was cochair for a Congressionally charged federal diabetes commission that made transformative recommendations for an all-of- govern-

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ment approach. He received the American Public Health Association's Everett M. Rogers Award for lifetime achievement in health communication science and WHO Non-Communicable Disease Policy award. He received an M.D. from the University of Pennsylvania.

Laura A. Schmidt, Ph.D., is a professor of health policy in UCSF School of Medicine. She holds a joint appointment in the Philip R. Lee Institute for Health Policy Studies and the Department of Humanities and Social Sciences. Dr. Schmidt seeks to understand how changing lifestyles are contributing to rising rates of chronic disease across the globe and what to do about it. Her work explores the growing pressures of globalizing economies, rising inequality, and commercial products that undermine our health. She works directly with policy makers to craft and implement evidence-based policies that reduce the consumption of ultraprocessed foods and other commercial products that harm human and planetary health. She received her Ph.D. in sociology at UC Berkeley, where she also completed doctoral coursework in public health.

Craig A. Umscheid, M.D., is a general internist and clinical epidemiologist who serves as the director of the EPC Division and senior science advisor at AHRQ. He is also an adjunct professor of Medicine at Georgetown University School of Medicine, where he practices clinically. Dr. Umscheid was an associate professor at the University of Chicago, where he served as the chief quality and innovation officer and vice president of health care delivery science, with oversight of clinical quality, medical informatics, and clinical innovation. His career has been dedicated to developing, implementing, and evaluating approaches to integrate research evidence into practice across provider organizations in the pursuit of improving the quality and value of patient care. This work has been supported by AHRQ, PCORI, the Centers for Disease Control and Prevention, and NIH. He earned an M.D. from Georgetown University.

Dr. Patricia Valdez, Ph.D., is a health science policy analyst at NIH and extramural research integrity officer in the NIH OER. She serves as a liaison between NIH and the HHS ORI and handles allegations of research misconduct in NIH-funded extramural activities. For the past 2.5 years, she has been involved in updating NIH grant applications and review language aimed at enhancing the reproducibility of biomedical science through rigor and transparency. Before OER, Dr. Valdez was the manager of publication ethics for the American Society for Biochemistry and Molecular Biology. She received her Ph.D. in molecular and cell biology from UC Berkeley.

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Tracey Woodruff, Ph.D., is a professor and director of UCSF PRHE. She is a leading scientist who has produced foundational research on how harmful chemicals and pollutants impact health, pregnancy, and child development, including the first international study to document the effects of air pollution and preterm birth and the first to document toxic chemicals in pregnant women and newborns. A national expert in chemical and regulatory policy, she was a senior scientist and policy advisor for the U.S. EPA's Office of Policy before UCSF. She earned a Ph.D. from USCF.

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Appendix C

Workshop Speaker Disclosures

Speaker*	Disclosures
Lisa Bero	No funding for this presentation. • Remuneration paid to University of CO for service as senior research integrity editor, *Cochrane* • Consulting fees—Canadian Health Products and Food Branch External Conflict of Interest (COI) Advisor • Grant funding: NHMRC #1139997, State of CO, Greenwall Foundation, NIHR • Prior grant funding: ORI, NIH, CA Tobacco-Related Disease Research Program, FAMRI, RWJ
Patricia Valdez	No relationships to disclose.

Daniel Greenbaum	Full-time employee of the Health Effects Institute, a 501c3 nonprofit research institute.
	HEI's funds, from which their compensation is drawn, come from
	• Core air pollution and health
	  ◦ The U.S. EPA (Offices of Air and Radiation and Research and development)
	  ◦ The Motor Vehicle industry (the 24 motor domestic and international vehicle and engine companies doing business in the United States)
	• Global Health
	  ◦ Clean Air Fund (London, England)
	  ◦ Children's Investment Fund Foundation (London, England)

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Clive Green	No relationships to disclose.
David Michaels	Salary: • Milken Institute School of Public Health of George Washington University • McElhattan Foundation (through GWU) Current relationships with potential conflicts of interest: ° Consultant for Asbestos Claimants' Committee—Georgia Pacific/Bestwall Bankruptcy; Agreed to be expert witness in Attorney General of the State of Mississippi v. Johnson & Johnson and Johnson &Johnson Consumer Companies, Inc. Funding support for the book *The Triumph of Doubt: Dark Money and the Science of Deception* (Oxford University Press, 2020) came from • Milken Institute School of Public Health of GWU • Forsythia Foundation • Passport Foundation • Broad Reach Fund of the Maine Community Foundation • Bauman Foundation • With additional support from the Rockefeller Foundation through a writing residency the Bellagio Center
Adrian Hernandez	Research American Regent; Amgen; Bayer; Boehringer Ingelheim; Merck; NIH: NIA, NCATS, NCCIH, NHLBI; Novartis; PCORI; Verily Consulting AstraZeneca; Biofourmis; Boston Scientific; Bristol Myers Squibb; Cytokinetics; Eidos Therapeutics; Intercept; Novartis; Novo Nordisk Editorial AMA: *JAMA Cardiology*
Laura Schmidt	No relationships to disclose.

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Speaker*	Disclosures
Martin McKee	• The work described in this presentation was undertaken in their role of editor in chief (unpaid) of the *European Journal of Public Health* (1998–2003) and while the speaker was, as now, a professor at the London School of Hygiene & Tropical Medicine. • President, British Medical Association & Past President European Public Health Association • Research director, European Observatory on Health Systems & Policies (partnership of WHO, EU, governments) • Research funding: Wellcome trust, UKRI, Horizon Europe, CIHR • No other relationships to declare
Adam Dunn	• Funding: The University of Sydney • Financial conflicts of interest: No relevant conflicts of interest to declare. • Member of the Society for Research Synthesis Methodology, including Membership Committee, Interim Trustee; Advisory Group for PROSPERO • Advisory for HealthBank and Andi Health (no remuneration) • Associate Editor, *Research Integrity & Peer Review*; Editorial Board Member, *JAMIA Open* • Program Committee and Senior Program Committee for computer science conferences including WebConf, WSDM, SIGKDD, ICWSM • Head of Department, Biomedical Informatics and Digital Health, Faculty of Medicine and Health, University of Sydney • Convener, Digital Health and Informatics Network, University of Sydney • Affiliate Faculty, Computational Health and Informatics Program, Boston Children's Hospital
Dean Schillinger	• Receives P30 funding from NIH to direct a Center for Diabetes Translational Research • Receives R01 funding from NIH to evaluate the effects of an SSB tax on consumption and to project population health impacts. • Receives CDC funding to evaluate the effects of SNAP on diabetes outcomes. • Received CA Department of Public Health and CDC funding to direct the CA Diabetes Prevention & Control Program • Reimbursed for serving as scientific expert to Federal 9th circuit Court in defense of a case involving ABA vs City and County of San Francisco (2015)
Sunita Sah	No conflicts of interest to declare.
Rita Redberg	No financial conflicts. Speaker's comments today are as an individual; they are not speaking for the JAMA Network. • Editor, *JAMA Internal Medicine* • Funding from Arnold Ventures LLC. NHLBI

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Speaker*	Disclosures
Quinn Grundy	No conflicts of interest to disclose. • Project board member on the Collaboration COI Policy for Cochrane Library Content Revision (2018–2019) • Serve as a member of the Conflict of Interest arbitration panel for the Cochrane Collaboration (2020–present) • Associate Editor for the journal *Cochrane Evidence Synthesis and Methods*, which has adopted the Cochrane COI Policy Other Industry relationships: • Fees for participating in clinical trials • Pharmaceutical grants for research • Pharmaceutical advisory board membership • Honoraria for attending meetings • Speaking fees for giving pharma funded talks • Pharmaceutical consulting fees • Travel expenses to attend conferences
Vincent Cogliano	The presenter's only professional compensation is from the State of California, but this presentation was developed outside of official time. The principles and processes discussed in this presentation were developed as part of the presenter's previous employment at the International Agency for Research on Cancer (IARC).
Craig Umscheid	• No financial conflicts of interest to disclose. • Employee of the Agency for Healthcare Research and Quality (AHRQ) in the U.S. Department of Health and Human services (HHS). • No statement in this presentation should be constructed as an official position of AHRQ or HHS. • Adjunct professor of medicine at Georgetown University School of Medicine and provides clinical care at MedStar Georgetown University Hospital.

*Panelist members who did not give an individual presentation did not report any disclosures.

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